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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2014

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number 001-36845

Bellerophon Therapeutics, Inc.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**47-3116175**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
53 Frontage Road Suite 301 Hampton, New Jersey	
(Address of Principal Executive Offices)	**08827** (Zip Code)

Registrant's telephone number, including area code: **(908) 574-4770**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common Stock, $0.01 par value per share	**NASDAQ Global Market**

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. ☐ Yes ☒ No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. ☐ Yes ☒ No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. ☐ Yes ☒ No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). ☐ Yes ☐ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer	Accelerated filer	Non-accelerated filer ☒ (Do not check if a smaller reporting company)	Smaller reporting company
☐	☐		☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). ☐ Yes ☒ No

The registrant's common stock began trading on the NASDAQ Global Market on February 13, 2015. As of February 13, 2015, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $63.1 million, based upon the closing price on the NASDAQ Global Market reported for such date. The registrant has elected to use February 13, 2015, the initial trading date of the registrant's common stock on the NASDAQ Global Market, as the calculation date because on June 30, 2014 (the last business day of the registrant's most recently completed second fiscal quarter), the registrant's common stock was not publicly traded. Shares of common stock held by each officer and director and by each person who is known to own 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares outstanding of the registrant's common stock, as of March 25, 2015: 12,905,392

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REFERENCES TO BELLEROPHON

In this Annual Report on Form 10-K, unless otherwise stated or the context otherwise requires:

- references to the "Company," "Bellerophon," "we," "us" and "our" following the date of the Corporate Conversion refer to Bellerophon Therapeutics, Inc. and its consolidated subsidiaries;
- references to the "Company," "Bellerophon," "we," "us" and "our" prior to the date of the Corporate Conversion refer to Bellerophon Therapeutics LLC and its consolidated subsidiaries; and
- references to the "Corporate Conversion" or "corporate conversion" refer to all of the transactions related to the conversion of Bellerophon Therapeutics LLC into Bellerophon Therapeutics, Inc., including the conversion of all of the outstanding units of Bellerophon Therapeutics, Inc. into shares of common stock of Bellerophon Therapeutics, Inc.

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our future results of operations and financial position, business strategy and plans and objectives of management for future operations, are forward-looking statements, are forward-looking statements. The words "may," "will," "should," "expects," "plans," "anticipates," "could," "intends," "target," "projects," "contemplates," "believes," "estimates," "predicts," "potential" or "continue" or the negative of these terms or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the timing of the ongoing and expected clinical trials of our INOpulse and BCM product candidates, including statements regarding the timing of completion of the trials and the respective periods during which the results of the trials will become available;
- the timing of and our ability to obtain marketing approval of our product candidates, and the ability of our INOpulse and BCM product candidates to meet existing or future regulatory standards;
- our ability to operate, and the implementation of our business strategy, as a stand-alone company;
- our ability to comply with government laws and regulations;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our estimates regarding the potential market opportunity for our product candidates;
- the timing of or our ability to enter into partnerships to market and commercialize our product candidates;
- the rate and degree of market acceptance of any product candidate for which we receive marketing approval;
- our intellectual property position;
- our expectations related to the use of proceeds from our initial public offering in February 2015;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional funding and our ability to obtain additional funding;
- the success of competing treatments;
- our competitive position; and
- our expectations regarding the time during which we will be an "emerging growth company" under the Jumpstart Our Business Startups Act of 2012.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ

materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information.

PART I

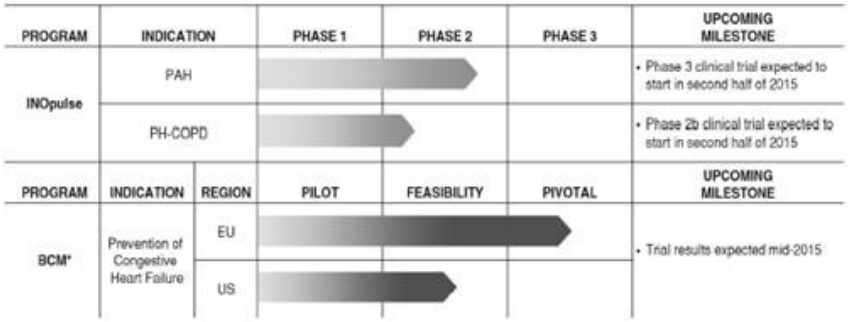
Item 1. Business

Overview

We are a clinical-stage therapeutics company focused on developing innovative products at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary and cardiac diseases. We have two programs in advanced clinical development. The first program, INOpulse, is based on our proprietary pulsatile nitric oxide delivery device. We are currently developing two product candidates under our INOpulse program: one for the treatment of pulmonary arterial hypertension, or PAH, for which we intend to commence Phase 3 clinical trials in the second half of 2015, and the other for the treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease, or PH-COPD, which is in Phase 2 development. Our second program is bioabsorbable cardiac matrix, or BCM, which is currently in a placebo-controlled clinical trial designed to support CE mark registration in the European Union. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure, and we expect to report top line results in mid-2015. Assuming positive results, we intend to conduct a pivotal pre-market approval trial of BCM beginning in the first half of 2016, which will be designed to support registration in the United States. We are developing BCM for the prevention of cardiac remodeling, which often leads to congestive heart failure following an ST-segment elevated myocardial infarction, or STEMI.

Our Product Candidates

The following table summarizes key information about our development programs and product candidates. We have worldwide commercialization rights to all of our product candidates.



* We are currently conducting a single clinical trial for BCM that, assuming positive results, we plan to use as a CE mark registration trial in the European Union and following which we would conduct a second, larger clinical trial to support registration in the United States.

From the inception of our business through December 31, 2014, $194.6 million was invested in our development programs. Prior to our recent initial public offering, our sole source of funding was investments in us by our former parent company, Ikaria, Inc., or Ikaria. As used in herein, unless context otherwise requires, references to "Ikaria" refer to Ikaria, Inc. and its subsidiaries and any successor entity.

INOpulse

Our INOpulse program is an extension of the technology used in hospitals to deliver continuous-flow inhaled nitric oxide. Use of inhaled nitric oxide is approved by the U.S. Food and Drug Administration, or the FDA, and certain other regulatory authorities to treat persistent pulmonary hypertension of the newborn. Ikaria has marketed continuous-flow inhaled nitric oxide as INOmax for hospital use in this indication since approval in 1999. In October 2013, Ikaria transferred to us exclusive worldwide rights to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and pulmonary hypertension associated with idiopathic pulmonary fibrosis, or PH-IPF, with no royalty obligations. Our INOpulse program is built on scientific and technical expertise developed for the therapeutic delivery of inhaled nitric oxide. In 2010, Ikaria filed an investigational new drug application, or IND, for INOpulse for the treatment of patients with PAH, which is a form of pulmonary hypertension that is closely related to persistent pulmonary hypertension of the newborn. In 2012, Ikaria filed a second IND for INOpulse for the treatment of patients with PH-COPD. These INDs were included in the assets that were transferred to us by Ikaria.

Nitric oxide is naturally produced and released by the lining of the blood vessel and results in vascular smooth muscle relaxation, an important factor in regulating blood pressure. As the muscles of the blood vessels relax, this allows the heart to increase blood flow to tissues and organs of the body, including the lung. When administered through inhalation, nitric oxide acts to selectively reduce pulmonary arterial pressure in the lung with minimal effects on blood pressure outside of the lungs, an important safety consideration.

Inhaled nitric oxide is widely used in the hospital setting for the treatment of a variety of conditions and, as reported by Ikaria, over 450,000 patients have been treated with inhaled nitric oxide worldwide since its first such use. However, chronic outpatient use of this therapy has previously been limited by a lack of a safe and compact delivery system for outpatient use. We have designed our INOpulse device, which is the means by which inhaled nitric oxide is delivered to the patient, to be portable, which enables use by ambulatory patients on a daily basis inside or outside their homes. Our INOpulse device has a proprietary mechanism that delivers brief, targeted pulses of nitric oxide timed to occur at the beginning of a breath for delivery to the well-ventilated alveoli of the lungs, which minimizes the amount of drug required for treatment. We estimate this, and the higher concentration of nitric oxide we use, reduces the volume of drug delivered to approximately 5% of the volume required for equivalent alveolar absorption using standard continuous flow delivery systems, and also reduces the amount of nitric oxide, as well as its by-product nitrogen dioxide, that is exhaled and released into the patient's environment. INOpulse is designed to automatically adjust nitric oxide delivery based on a patient's breathing pattern to deliver a constant and appropriate dose of the inhaled nitric oxide over time, independent of the patient's activity level, thus ensuring more consistent dosing of the nitric oxide to the alveoli of the lungs.

In our recently completed INOpulse clinical trials, we used the first generation INOpulse device, which we refer to as the INOpulse DS device. In future clinical trials, we intend to use our second generation device, which we refer to as the Mark2. The Mark2 has approximately the same dimensions as a paperback book and weighs approximately 2.5 pounds. The Mark2 has a simple and intuitive user interface and a battery life of approximately 24 hours when recharged, which takes approximately four hours and can be done while the patient sleeps. Based on the doses we have evaluated in our clinical trials, we expect that the cartridge will need to be replaced once a day. In addition, we have developed a triple-lumen nasal cannula, which forms part of the Mark2 and enables more accurate dosing of nitric oxide and minimizes infiltration of oxygen, which can react with nitric oxide to form nitrogen dioxide. Our triple-lumen nasal cannula consists of a thin, plastic tube that is divided into three channels from end-to-end, including at the prongs that are placed in the patient's nostrils, with one channel delivering inhaled nitric oxide, a second for breath detection and a third available for oxygen delivery. INOpulse is designed to be compatible with many long-term oxygen therapy, or LTOT, systems. In the usability research we conducted, all eight patients with experience with the INOpulse DS device responded positively to the Mark2, and several of these patients indicated that the ability to take the Mark2 outside the home would likely reduce concerns with maintaining compliance.

Our technology is based on patents we have exclusively licensed from Ikaria for the treatment of PAH, PH-COPD and PH-IPF. These include patents with respect to the pulsed delivery of nitric oxide to ensure a consistent dose over time, which expire as late as 2027 in the United States and as late as 2026 in certain other countries, as well as with respect to the special triple-lumen cannula that allows for safer and more accurate dosing of pulsed nitric oxide, which expires in 2033. We have also licensed several other patent applications from Ikaria for certain of the innovations included in the Mark2 and certain of the resulting patents, if issued, would expire as late as 2033.

INOpulse for PAH

We are developing INOpulse for the treatment of PAH to address a significant and unmet medical need in an orphan disease, which is a disease that affects fewer than 200,000 individuals in the United States. This program represents a potential first-in-class therapy for this indication. In October 2014, we completed a randomized, placebo-controlled, double-blind Phase 2 clinical trial of INOpulse for PAH. The data from this trial showed trends toward lower pulmonary vascular resistance in both active arms compared to placebo and a slight trend toward increased six-minute walk distance in the higher dose group. While neither result reached the threshold for statistical significance, additional exploratory analyses of patients who were compliant with therapy, assessed as being on therapy for greater than 12 hours per day, as well as a similar analysis of patients on LTOT showed clinically meaningful and statistically significant improvements in both the primary endpoint of pulmonary vascular resistance and the key secondary endpoint of six-minute walk distance, relative to placebo, for patients on the higher dose. These two sub groups each comprised more than 50% of the total patients enrolled in the trial. Statistical significance for clinical trials means that, should the trial have a positive outcome, the results have a low probability of having occurred because of chance rather than from the efficacy of the product.

We believe the results of this trial provide sufficient indication of clinical benefit and safety to continue development of INOpulse for PAH in pivotal Phase 3 clinical trials. We had an End of Phase 2 meeting with the FDA on January 8, 2015. Based on feedback from the FDA at this meeting, we are moving forward with Phase 3 development and plan to conduct two adequate and well-controlled confirmatory Phase 3 clinical trials, either sequentially or in parallel. In March 2015, we requested feedback on the proposed trial design from the Scientific Advice Working Party of the European Medicines Agency, or the EMA. We intend to finalize the clinical trial design following additional discussions with the FDA as well as with other regulatory authorities, including with the EMA.

The FDA has granted orphan drug designation to our nitric oxide program for the treatment of PAH. If a product with an orphan drug designation is the first to receive FDA approval, the FDA will not approve another product for the same indication that uses the same active ingredient for seven years, unless the other product is shown to be clinically superior.

PAH is characterized by abnormal constriction of the arteries in the lung that increases the blood pressure in the lungs which, in turn, results in abnormal strain on the heart's right ventricle, eventually leading to heart failure. While prevalence data varies widely, we estimate there are a total of at least 35,000 patients currently diagnosed with and treated for PAH in the United States and European Union. Moreover, because PAH is rare and causes varied symptoms, we believe there is significant under-diagnosis of the condition at its early stages. There are several approved therapies for PAH, and we estimate, based on public product sales data, that 2012 combined global sales for these therapies were over $4.0 billion. Most PAH patients are treated with multiple medications and many are on supportive therapy. We believe that approximately 20,000 patients have severe to very severe PAH and are treated with multiple therapies, including LTOT. Despite the availability of multiple therapies for this condition, PAH continues to be a life-threatening, progressive disorder. A French registry initiated in 2002 and a U.S. registry initiated in 2006 estimate that the median survival of patients with PAH is three and five years from initial diagnosis, respectively.

INOpulse for PH-COPD

We are also developing INOpulse for the treatment of PH-COPD. The data from an initial three-month, open-label chronic-use Phase 2 trial conducted by a third party, which we in-licensed, showed that pulsed inhaled nitric oxide significantly reduced pulmonary arterial pressures in PH-COPD patients on LTOT and did so without causing hypoxemia, or an abnormally low level of oxygen in the blood, which is a significant concern for these patients. In June 2012, Ikaria submitted the data from this trial to the FDA as part of the IND package for INOpulse for PH-COPD. Based on discussions with the FDA, we believe this trial is an adequate Phase 2 trial. The FDA asked us to confirm the dose range and the safety related to hypoxemia in PH-COPD patients using the INOpulse device, prior to proceeding to large scale trials. Following this guidance, we conducted a Phase 2 acute dose ranging randomized placebo-controlled trial in 159 patients with the INOpulse DS device, with doses ranging from 3 mcg to 75 mcg. This trial, which we completed in July 2014, identified a dose range that showed similar reduction in pulmonary arterial pressure versus baseline when compared to the initial acute effects of pulsed inhaled nitric oxide in the original chronic-use trial. In addition, in our confirmatory trial, none of the INOpulse doses tested had an adverse effect on hypoxemia relative to placebo. While the reduction in pulmonary arterial pressure did not reach statistical significance versus placebo in this acute setting, which was the primary endpoint of the trial, we believe that the results have confirmed a dose range for this therapy that delivers a significant reduction in pulmonary arterial pressure versus baseline and does not cause hypoxemia in patients with PH-COPD. We are currently evaluating our trial design for chronic use in this population in a three-month Phase 2b trial and plan to finalize the protocol following discussions with regulatory authorities in the United States and European Union.

COPD is a disease characterized by progressive and persistent airflow limitations. Patients with more severe COPD frequently have hypoxemia and may be treated with LTOT. Despite treatment with oxygen, hypoxemia can progress and contribute to pulmonary hypertension. In 2010, Datamonitor estimated that over 1.4 million COPD patients in the United States were being treated with LTOT. Based on academic studies, we estimate that 50% of COPD patients on LTOT have pulmonary hypertension. PH-COPD patients have a lower median life expectancy and a higher rate of hospitalization than COPD patients with similar respiratory disease but without pulmonary hypertension. Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant.

BCM

Our second program, BCM, is a medical device intended to prevent congestive heart failure following a STEMI, which is a type of severe heart attack. Patients who suffer a STEMI are at an increased risk for congestive heart failure due to potential cardiac remodeling, which is a structural change in the size and shape of the heart that affects its ability to function normally.

BCM is delivered during a minimally invasive, commonly performed cardiac procedure called a percutaneous coronary intervention procedure. BCM is a formulated sterile solution of sodium alginate and calcium gluconate designed to be administered as a liquid through the coronary artery. When administered following a STEMI, BCM flows into damaged heart muscle where, in the presence of abnormally high extracellular calcium released by the damaged cells, it forms a protective hydrogel meshwork within the wall of the heart's left ventricle. Based on pre-clinical animal studies, we believe that BCM has the potential to act as a flexible scaffold to provide physical support to the ventricle wall in the early stages of recovery following a STEMI and prevent further structural damage while the heart muscle heals. In addition, in our pre-clinical animal studies, as calcium levels in the damaged area returned to normal, BCM dissolved and was excreted through normal kidney function.

In a 27-patient pilot clinical trial conducted in 2009, BCM was safely administered within seven days following a STEMI. Patients showed no deterioration from baseline of important measures of left ventricular function at one, three and six month measurements. Follow-up safety data for these patients, which was obtained four years after the completion of the pilot clinical trial, showed one death from T-cell lymphoma—likely a

preexisting condition—and one hospitalization from congestive heart failure. One patient was lost to follow-up in year four, but this patient had no device related adverse events through the three-year evaluation. These results were below the incidence of adverse events of approximately 25% to 30% we expected for patients following an acute myocardial infarction, or AMI, commonly known as a heart attack. This expectation was based on our review of publicly reported data from two long-term third-party studies of AMI patients.

We initiated a clinical trial of BCM in December 2011 and enrolled the first patient in April 2012. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure at almost 90 clinical sites in Europe, Australia, North America and Israel. We expect to report top line results in mid-2015, following a six-month follow-up period for all patients. This trial is a CE mark registration trial in the European Union. If the results of this trial are positive, we expect it would form the basis for our application for CE marking in the European Union and we would expect to conduct a second, larger clinical trial to support approval in the United States through the premarket approval, or PMA, pathway.

In the United States, we are developing BCM under an investigational device exemption, or IDE. We sponsored an IDE application for our ongoing feasibility clinical trial of BCM to prevent ventricular remodeling and heart failure in patients who are at high risk for ventricular remodeling after an AMI and a successful percutaneous coronary intervention. The FDA has designated BCM as a Class III device. Class III devices are those which the FDA deems to pose the greatest risk, such as those that are life sustaining or life supporting. As a result, the FDA regulates Class III devices under the most rigorous device approval pathway, the PMA process. Device approval under the PMA pathway must be supported by extensive data, including from pre-clinical studies and clinical trials, that demonstrate the safety and efficacy of the device for its intended use. In August 2013, the FDA confirmed that no additional pre-clinical studies were required to support a PMA application. Assuming positive results from this trial, we intend to conduct a pivotal pre-market approval trial of BCM beginning in the first half of 2016, which will be designed to support registration in the United States.

We have an exclusive worldwide license to BCM from BioLineRx Ltd. and its subsidiary, or BioLine, including with respect to issued composition of matter patents on BCM that expire as late as 2029 in the United States, with a possible patent term extension to 2032 to 2034 depending on the timing of marketing approval and other factors, and 2024 in certain other countries. We licensed this product candidate in 2009, following completion of the 27-patient pilot clinical trial conducted by BioLineRx Ltd.

Data from the American Heart Association and the European Association for Percutaneous Cardiovascular Interventions suggests that a total of over 1,900,000 patients suffer a heart attack in the United States and European Union each year, with at least 750,000 of these patients having a STEMI. Following a STEMI, patients are at increased risk of developing cardiac remodeling and subsequent congestive heart failure, and data from long-term third-party studies suggest that the five-year post-AMI rate of congestive heart failure or death is approximately 35% to 40%.

Our Strategy

Our goal is to become a leader in developing and commercializing innovative products at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary and cardiac diseases. The key elements of our strategy to achieve this goal include:

- *Advance the clinical development of INOpulse.* One of our lead product candidates is INOpulse for PAH. Based on the results from our recently completed Phase 2 clinical trial in PAH, we intend to initiate a Phase 3 clinical trial for this indication in the second half of 2015. In addition, we believe the results of the PH-COPD clinical trials support continued Phase 2 development and we plan to evaluate our options for further development, including potentially through partnerships.

- *Advance the clinical development of BCM in the prevention of cardiac remodeling following a STEMI.* One of our other lead product candidates is BCM. Assuming positive results from our

ongoing clinical trial, we expect to file for CE marking in the European Union in the second half of 2015 and to initiate a pivotal trial in early 2016 to support a PMA submission seeking marketing approval in the United States.

- *Leverage our historical core competencies to expand our pipeline.* We have years of institutional experience in the use of inhaled nitric oxide in treating pulmonary hypertension and in the development of drug-device combination product candidates. If we successfully advance INOpulse for the two product candidates we are currently developing, we expect to develop INOpulse for treatment of PH-IPF and, subject to obtaining additional license rights from Ikaria, potentially other outpatient pulmonary hypertension indications. Our longer-term vision is to identify and opportunistically in-license innovative therapies that are at the intersection of drugs and devices and to develop and commercialize these product candidates.

- *Build commercial infrastructure in select markets.* As we near completion of the development of our product candidates, we expect to build a commercial infrastructure to enable us to market and sell certain of our product candidates with a specialized sales force and to retain co-promotion or similar rights, when feasible, in indications requiring a larger commercial infrastructure. While we may partner with third parties to commercialize our product candidates in certain countries, we may also choose to establish commercialization capabilities in select countries outside the United States.

INOpulse

INOpulse Scientific Background

Nitric oxide is a naturally occurring molecule produced by many cells of the body. Researchers found that nitric oxide is produced and released by the lining of the blood vessel and plays a role in controlling muscle tone in blood vessels. In particular, nitric oxide results in vascular smooth muscle relaxation in blood vessels and thus is an important factor in regulating blood pressure. As the muscles of the blood vessels relax, blood flow increases, helping the heart to deliver more blood to the body. When administered by inhalation to patients with pulmonary hypertension, we expect inhaled nitric oxide to act in a similar manner to naturally produced nitric oxide.

The scientific journal *Science* named nitric oxide Molecule of the Year in 1992. Additionally, the three researchers who discovered the role of nitric oxide as a signaling molecule in the cardiovascular system earned the Nobel Prize for Physiology or Medicine in 1998.

In 1991, Dr. Warren Zapol and his associates at the Massachusetts General Hospital discovered that inhaling nitric oxide in gas form could reduce high blood pressure in the lungs, a condition known as pulmonary hypertension. Nitric oxide is a rapid and potent vasodilator, which means it dilates, or widens, blood vessels. When inhaled, it quickly dilates blood vessels in the lungs, which reduces blood pressure in the lungs, strain on the right ventricle and shunting of de-oxygenated blood away from the lungs. Because more blood can flow through the lungs, blood levels of oxygen improve. In addition, inhaled nitric oxide improves the efficiency of oxygen delivery, and because it is a gas, it goes only to the portions of the lung that are ventilated, or receiving air flow, and increases blood flow only in these areas. Thus, inhaled nitric oxide improves ventilation-perfusion matching, an important element of lung function involving the air that reaches the lungs, or ventilation, and the blood that reaches the lungs, or perfusion. Inhaled nitric oxide is quickly inactivated after contact with blood, and is selective for the lungs, meaning that it has minimal effects on blood pressure outside of the lungs, which is an important safety consideration.

In 1999, the FDA approved the use of inhaled nitric oxide for the short-term treatment of persistent pulmonary hypertension of the newborn. Based on this approval, and similar approvals from foreign regulatory authorities, continuous-flow inhaled nitric oxide, which is administered to ventilated patients by a dedicated in-hospital device, is marketed by Ikaria and its commercialization partners worldwide as INOmax (INOflo in

Japan). Inhaled nitric oxide is widely used in the hospital setting for a variety of conditions and, as reported by Ikaria, over 450,000 patients have been treated with inhaled nitric oxide worldwide since its commercial launch. However, chronic outpatient use of this therapy has previously been limited by the lack of a safe and compact delivery system for outpatient use.

INOpulse Drug-Device Combination

Our INOpulse device has a proprietary mechanism that delivers brief, targeted pulses of nitric oxide, timed to occur at the beginning of a breath and targeted for delivery to the well-ventilated alveoli of the lungs. INOpulse is portable and therefore allows for treatment of ambulatory patients on a daily basis inside or outside their homes. INOpulse is designed to automatically adapt based on a patient's breathing pattern to deliver a constant dose of the drug over time, independent of the patient's activity level, thus ensuring predictable dosing in the alveoli of the lungs. We estimate that, because of the pulsed delivery and higher concentration of nitric oxide we use, the volume of drug delivered is reduced to approximately 5% of the volume required for equivalent alveolar absorption using standard continuous-flow delivery systems.

INOpulse is configured to be highly portable and compatible with available modes of LTOT via nasal cannula delivery. Our recently completed clinical trials of INOpulse for PAH and INOpulse for PH-COPD utilized the first generation INOpulse DS device, which is derived from an older hospital-based system. While this device is portable and appropriate for use at home, to make INOpulse acceptable to a broader range of patients and to improve its usability, we are near completion of our second generation device, the Mark2, which we plan to use in future clinical trials.

The Mark2 is approximately the size of a paperback book and weighs approximately 2.5 pounds. It has a simple user interface and a battery life of approximately 24 hours when recharged, which takes approximately four hours and can be done while the patient sleeps. Based on the doses we evaluated in our clinical trials, we expect the cartridge will need to be replaced once a day. The Mark2 incorporates our proprietary triple-lumen nasal cannula, safety systems and proprietary software algorithms. The triple-lumen nasal cannula enables more accurate dosing of inhaled nitric oxide and minimizes infiltration of oxygen, which can react with nitric oxide to form nitrogen dioxide. Our triple-lumen nasal cannula consists of a thin, plastic tube that is divided into three channels from end-to-end including at the prongs that are placed in the patient's nostrils, with one channel delivering inhaled nitric oxide, a second for breath detection and a third available for oxygen delivery. Our device is designed to be compatible with many LTOT systems.

The Mark2 has been well received by patients in the usability research we have conducted. In addition to the baseline testing on the original INOpulse DS device, we have conducted two rounds of testing with COPD and PAH patients to evaluate the user interface, loading mechanism, size, carrying bag and other features. In the usability research we have conducted, all eight patients with experience with the INOpulse DS device responded positively to the Mark2, and several of these patients indicated that the ability to take the Mark2 outside the home would likely reduce concerns with maintaining compliance.

Based on discussions with the FDA, we are required to show that the amount and timing of inhaled nitric oxide delivery is similar across INOpulse device generations. We have developed a regulatory bridging strategy to meet these requirements. To facilitate the transition from our existing INOpulse DS device to the Mark2 in our INOpulse clinical program, we plan to conduct comparability testing of inhaled nitric oxide dosing with the Mark2 as compared to the INOpulse DS device. This testing will include a comparison of critical parameters, including pulse width and nitric oxide output. We will also assess whether the Mark2 will meet the performance specifications of the INOpulse DS device in addition to Mark2-specific requirements. In addition, we are developing a bridging test report that we expect to include in the regulatory package that we anticipate submitting to the FDA during the first half of 2015 to gain approval for the device transition. We discussed our bridging strategy with the FDA during a meeting in May 2013, and we believe that, assuming the Mark2 meets the specified comparability parameters, this testing will be sufficient to gain FDA approval to use the Mark2 in future clinical trials, as planned.

We have licensed from Ikaria several patents and patent applications for certain innovations in our INOpulse devices. These include patents with respect to the pulsed delivery of inhaled nitric oxide to ensure a consistent dose over time, which expire as late as 2027 in the United States and as late as 2026 in certain other countries, as well as a patent with respect to the triple-lumen cannula that allows for safer and more accurate dosing of pulsed inhaled nitric oxide, which expires in 2033. We have also licensed several other patent applications from Ikaria for certain of the innovations included in the Mark2 and certain of the resulting patents that, if issued, would expire as late as 2033.

In the European Union, where there is no formal drug-device designation, we expect INOpulse to be evaluated by the EMA as a drug with specific reference in the label to the device and cannula, which will require a separate CE mark from a Notified Body.

Introduction to Pulmonary Hypertension

Pulmonary hypertension is a disease characterized by constriction of the blood vessels in the lung, which causes blood pressure in the lung to rise and, in turn, increases the work required for the right ventricle of the heart to pump blood. The World Health Organization, or WHO, has endorsed a consensus classification for pulmonary hypertension that was updated most recently in 2013. The WHO classification has five broad pulmonary hypertension groups based on similarities in pathological and hemodynamic characteristics and therapeutic approaches. We are initially focusing development of INOpulse in indications included in WHO Groups 1 and 3 due to our view of the likelihood of success and the size and commercial viability of these markets. Group 1 pulmonary hypertension is comprised of patients with pulmonary arterial hypertension and is referred to as PAH. This Group combines conditions with a range of causes, all of which have a characteristic pattern of vascular remodeling. The constriction of the blood vessels and the resulting pressure on the heart is often the major reason for poor prognosis of PAH patients since they can be otherwise healthy. Most PAH-specific medications are vasodilators and work through one of the three key mechanistic pathways for vasoconstriction and vasodilation. We expect that, because inhaled nitric oxide is a vasodilator, patients in Group 1 will benefit from INOpulse. Group 3 pulmonary hypertension consists of pulmonary hypertension associated with lung disease or hypoxemia, which is an abnormally low level of oxygen in the blood. This Group includes patients with PH-COPD and PH-IPF, among others.

INOpulse for Pulmonary Arterial Hypertension

We are developing INOpulse for PAH to address a significant and unmet medical need in an orphan disease. This product candidate represents the development of a potential first-in-class therapy for this indication. Although current therapy for PAH provides some therapeutic benefit, there remains no cure, and approved therapies can have significant systemic side effects, such as hypotension and liver injury. INOpulse for PAH is designed to be a selective, short-acting pulmonary vasodilator and is being tested as an add-on therapy to existing PAH medications to evaluate its efficacy and side effect profile, in particular its ability to provide clinical benefit without adding to the systemic effects such as hypotension.

Disease Background and Market Opportunity

PAH is a life-threatening, progressive disorder characterized by abnormally high blood pressure, or hypertension, in the pulmonary artery, the blood vessel that carries blood from the heart to the lungs. PAH occurs when most of the very small arteries, or arterioles, throughout the lungs narrow in diameter, which increases the resistance to blood flow through the lungs. To overcome the increased resistance, pressure increases in the pulmonary artery and the right ventricle, which is the heart chamber that pumps blood into the pulmonary artery. In addition, PAH may cause changes to the blood vessel lining that hinder the natural production of nitric oxide. Signs and symptoms of PAH occur when this increased pressure in the right ventricle cannot fully overcome the elevated resistance.

There are a number of drugs approved for the treatment of PAH that work primarily by reducing pulmonary vascular resistance, which is the primary problem for these patients. However, despite the availability of multiple therapies for this condition, the mortality rate for PAH remains high, with estimates of median survival ranging from three to five years. Patients with PAH also report severe impairment of health-related quality of life, including poor general and emotional health and impaired physical functioning. The most common symptoms of PAH are shortness of breath during exertion and syncope, or fainting spells. People with PAH may experience additional symptoms, particularly as the condition worsens, including dizziness, swelling of the ankles or legs, chest pain and a racing pulse. These impairments to health-related quality of life are comparable and sometimes more severe than those reported in patients with severely debilitating conditions such as spinal cord injury.

Since PAH is an orphan condition with poor diagnosis rates, published prevalence estimates for PAH vary widely. Based on epidemiological studies and current treatment rates, we estimate that there are a total of at least 35,000 patients currently diagnosed and treated for PAH in the United States and European Union. The average age of PAH patients at diagnosis is approximately 50 years, and approximately 80% of PAH patients are female. PAH is often diagnosed late in the disease progression with approximately 73% of these patients already having progressed to WHO functional Class III or IV at the time of diagnosis.

PAH is characterized by abnormal constriction of the arteries in the lung. PAH patients are generally treated with one or more of the four major classes of approved medications, which are prostacyclin and prostacyclin analogs, phosphodiesterase type-5 inhibitors, endothelin receptor antagonists and a soluble guanylate cyclase stimulator, all of which potentially result in vasodilatory systemic effects and, therefore, hypotension. Current guidelines recommend treatment with multiple medications in Class III and IV patients with progressive disease but suggest treatment be carefully managed by experienced physicians. Approximately 45% of PAH patients are treated with more than one class of medication at a given time. In addition, since hypoxemia can be a problem in these patients, it is often treated with LTOT in accordance with broadly supported treatment guidelines in the United States and European Union.

We are testing INOpulse for PAH as an add-on therapy for use in patients whose disease is progressing and who use additional medications. If it is approved, we expect INOpulse will provide the greatest benefit to patients who require pulmonary arterial pressure reductions beyond the reductions achieved with the medication they are already using. Because of its localized effect and short-half life, we do not expect INOpulse will add to systemic blood pressure reductions of other PAH drugs. We believe that INOpulse is also likely to be preferentially prescribed for patients already on LTOT. Data from a U.S. and a French registry indicate that approximately 40% of patients are treated with oxygen at diagnosis for hypoxemia. Approximately 60% of the patients from our recently completed Phase 2 clinical trial were on LTOT. We believe that, as compared to patients who are not using a nasal cannula, patients who are accustomed to using a nasal cannula for delivery of oxygen are more likely to be prescribed and are more likely to be compliant with the use of INOpulse.

A 2013 report by CVS Caremark Specialty Analytics provided examples of PAH medications with annual prices ranging from approximately $100,000 to $150,000 per patient per year in the United States. We expect that, if approved, the price of INOpulse will be in the range of other established PAH medications.

Scientific Rationale for Use of INOpulse for PAH

Since the discovery of the significant role of nitric oxide in vasodilation, there has been an expectation in the scientific community that inhaled nitric oxide could be an effective therapy for PAH. According to the Cleveland Clinic Center for Continuing Education section on Pulmonary Hypertension, exogenous administration of nitric oxide by inhalation is probably the most effective and specific therapy for PAH, but cost and technical complexity of delivering inhaled nitric oxide have limited its use to the hospital. Although not approved for the treatment of PAH, data from an in-hospital survey conducted by Ikaria showed an estimated 1,000 to 2,000 INOmax uses in PAH patients in the United States each year, indicating that physicians already use nitric oxide in some PAH patients. The difficulty in delivering inhaled nitric oxide outside of the hospital

results from the size of the device and cylinder and the need for a specialized delivery system with built-in safety systems.

We are developing nitric oxide for treatment of PAH because nitric oxide is a proven vasodilator, and PAH is primarily a disease of high pulmonary vascular resistance. PAH is associated with impaired release of nitric oxide and thus we believe chronic administration of inhaled nitric oxide may be viewed as an adjunctive or replacement therapy in patients with PAH. The use of inhaled nitric oxide in PAH has been proposed since the role of nitric oxide in this disease was identified. This drug has been tested in limited investigational studies conducted at academic institutions.

One clinical trial conducted at an academic center in Spain in 11 patients, seven of whom had severe PAH and four of whom had severe chronic thromboembolic pulmonary hypertension, or CTEPH, evaluated the use of pulsed inhaled nitric oxide in an ambulatory setting. In this open-label, single-arm trial with no placebo control, patients were given ambulatory pulsed inhaled nitric oxide therapy via a nasal cannula for up to one year, after being withdrawn from PAH-specific therapy. The nitric oxide pulse was delivered to the patient at the beginning of each inspiration at a flow rate that was individualized for such patient. The goal of this trial was to evaluate the efficacy and safety of long-term treatment with inhaled nitric oxide outside the hospital setting.

At the start of this trial, patients were evaluated for various measures including the distance they were able to walk in six minutes and WHO functional class. At baseline, most of these patients had significant impairment of six-minute walk distance, with the ability to walk an average of 125 meters, and poor WHO functional class status, with nine patients in Class IV and two patients in Class III. After one month of therapy, overall, patients improved based on WHO functional class, with six patients in Class III and five in Class II, and had improvements in six-minute walk distance of 128 meters on average. After six months of treatment, patients did not worsen clinically, however, between months six and 12, seven patients were given a phosphodiesterase type-5 inhibitor due to clinical worsening. One patient who initially did well with the added phosphodiesterase type-5 inhibitor therapy developed severe right heart failure at month eight and died, and another patient received a lung transplant at month nine. The remaining nine patients all had clinical status at month 12 similar to their one month evaluation, and improvements in functional class and six-minute walk distance for the group persisted over time.

We do not expect INOpulse to have systemic effects beyond the pulmonary vasculature because of the short half-life of nitric oxide combined with its targeted delivery to the alveoli. When nitric oxide is delivered as a pulse at the beginning of inhalation, it travels to the alveoli where it diffuses rapidly across the alveolar capillary membrane into the adjacent vascular smooth muscle of pulmonary vessels. This transport is similar to the natural transport of endogenous nitric oxide from the endothelial cells, where it is produced, to the vascular smooth muscle cells where it relaxes the muscle and causes vasodilation of the pulmonary arteries. We believe this makes INOpulse unlikely to have intolerable side effects, such as systemic hypotension or drug-drug interactions. Given the need for PAH patients to be treated with multiple therapies and the potential for increased hypotension from each of the currently approved PAH therapies, we are developing INOpulse as an add-on or adjunctive therapy for PAH, where we believe it has the highest commercial potential.

Clinical Development Program

INOpulse for PAH is designated as a drug-device combination by the FDA and is being evaluated through the Division of Cardiovascular and Renal Products of the Center for Drug Evaluation and Research with consultation from the Center for Devices and Radiological Health. For our IND for PAH, we submitted data from animal studies in rats and sheep as well as the results of a Phase 1 trial of pulsed inhaled nitric oxide in healthy volunteers. In addition, we referenced additional data from Ikaria's new drug application, or NDA, in respect of INOmax. Based on this, the FDA has agreed that no further preclinical studies are required for clinical development of INOpulse for PAH.

In the European Union, where there is no formal drug-device designation, we expect that INOpulse for PAH will be evaluated by the EMA as a drug with specific reference in the label to the device and cannula, which will require a separate CE mark from a Notified Body.

Phase 2 Clinical Trial

We recently completed Part A of our ongoing Phase 2 clinical trial of INOpulse for PAH in the United States and Canada. Our key inclusion criteria for patients in this trial were that they:

- be diagnosed with pulmonary hypertension WHO Group 1;
- be on at least one other PAH medication for at least 12 weeks prior to treatment with INOpulse; and
- demonstrate being able to walk between 100 and 450 meters within six minutes.

In addition, this trial excluded patients with evidence of significant left ventricular dysfunction.

The trial is being conducted in two parts, Part A and Part B. In October 2014, we completed Part A of this trial which was a randomized, placebo-controlled, double-blind clinical trial with patients randomized 1:1:1 to placebo or to one of two active doses, either 25 or 75 mcg/kg ideal body weight/hour, or mcg, for 16 weeks. Part B is an ongoing double-blind long-term extension of the initial trial with all patients on one of two doses of INOpulse for PAH to monitor the long-term safety and tolerability of the therapy. Eighty-one percent of the patients in Part A elected to enter the Part B long-term extension trial. The primary endpoint in this trial was a change in pulmonary vascular resistance from baseline at 16 weeks, which was the end of Part A. The target change in pulmonary vascular resistance was 190 dynes sec. cm-5, and the trial was powered for statistical significance at 130 dynes sec. cm-5. The main secondary endpoint was change in six-minute walk distance over the same period. A clinically meaningful change in six-minute walk distance is typically considered to be an increase of at least 30 to 35 meters. We expect to continue the ongoing Part B of this trial until the earliest of INOpulse for PAH being approved, clinical development of INOpulse for PAH being discontinued or our decision to discontinue Part B.

We typically use, and have used for this trial, a conventional method of assessing statistical significance known as a one-way analysis of variance, or ANOVA. In this method the threshold of statistical significance is reached when a measure known as the p-value is 0.05 or lower. Because we are using two doses, we are using a common adjustment to the significance threshold for the analysis in this trial, including the subgroup analysis, by requiring the p-value to be 0.025 or lower before it is considered significant. When the p-value is higher than this threshold it is considered that any directional benefit seen in the clinical trial could be due to chance rather than being a true measure of the efficacy of the product tested.

We randomized 80 patients for Part A of the Phase 2 clinical trial. The majority of the patients were female (79%), white (89%) and had idiopathic PAH (74%). The results from Part A of this trial, which are summarized in the table below, showed trends toward lower pulmonary vascular resistance in both the active arms compared to placebo and a slight trend toward increased six-minute walk distance in the higher dose group. However, neither result was statistically significant.

INOpulse for PAH—Phase 2 Part A Trial Results for All Patients

			Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
Parameter		**Placebo**	**25**	**75**
Total number of patients randomized		26	27	27
Pulmonary Vascular Resistance (dynes sec. cm-5)	Number analyzed	24	23	24
	Baseline (mean)	601.5	665.8	662.9
	Change from Baseline (mean)	47.2	-54.1	-15.0
	p-value (ANOVA)	—	0.091	0.178
6-Minute Walk Distance (m)	Number analyzed	24	24	23
	Baseline (mean)	367.5	326.8	300.7
	Change from Baseline (mean)	7.5	4.7	22.8
	p-value (ANOVA)	—	0.851	0.314

In an analysis of baseline characteristics, patients randomized to placebo were younger and less sick than those on either of the active arms on many dimensions including baseline pulmonary vascular resistance, baseline six-minute walk distance, duration of disease and WHO severity class. In addition, fewer of the patients on placebo were on LTOT compared to either of the active arms with more patients on LTOT at the 75 mcg dose than on the 25 mcg dose.

INOpulse for PAH—Phase 2 Trial Baseline Demographics

		Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
	Placebo	25	75
Number of patients	26	27	27
Age (years) (mean)	52.0	56.3	57.9
WHO Severity (number in Classes III and IV)	19	21	23
Disease duration (years) (mean)	5.5	6.2	6.0
Pulmonary Vascular Resistance (dynes sec.cm-5) (mean)	601.5	665.8	662.9
6-Minute Walk Distance (m) (mean)	367.5	326.8	300.7
Use of LTOT	46.2%	59.3%	77.8%

During evaluation of the data, we observed that adherence to therapy was widely variable. LTOT was a pre-specified parameter recorded at baseline, and patients using LTOT at baseline were more adherent to using the device. Good adherence was retrospectively defined as an average use of greater than 12 hours per day. Specifically, patients using LTOT had a rate of 70% adherence as compared with 33% adherence in those patients not using LTOT. Based on this observation, we conducted non-scheduled, exploratory analyses by LTOT use and by compliance (defined as patients who had average daily use of 12 hours per day or more). Each of these subgroups comprised more than 50% of the total patients enrolled in the trial. The results of these analyses are summarized in the following table.

INOpulse for PAH—Phase 2 Part A Trial Compliance to Therapy

	Percent of patients		
Average hours of use per day	All patients	On LTOT	Not on LTOT
< 4 Hours	6.3%	4.1%	9.7%
4-8 Hours	20.0%	8.2%	38.7%
8-12 Hours	17.5%	16.3%	19.4%
12-16 Hours	22.5%	30.6%	9.7%
16-20 Hours	16.3%	22.4%	6.5%
≥ 20 Hours	17.5%	18.4%	16.1%

Among LTOT users, there was a clinically meaningful and statistically significant improvement versus placebo in both pulmonary vascular resistance and six-minute walk distance in patients at the 75 mcg dose and there was a statistically significant improvement in pulmonary vascular resistance and a positive trend in change in six-minute walk distance in patients on the 25 mcg dose.

In the subgroup of compliant patients who used INOpulse for an average of greater than 12 hours per day, the results were very similar to those of the LTOT subgroup. This was expected since there is a significant overlap between the compliant patient and the LTOT group, with approximately 80% of compliant patients also treated with LTOT at baseline. In the compliant group, when compared to placebo, there was a positive trend for change in pulmonary vascular resistance and a clinically meaningful and statistically significant improvement in six-minute walk distance in the 75 mcg dose arm and there was a statistically significant improvement in pulmonary vascular resistance and a non-significant change in six-minute walk distance in the 25 mcg dose arm.

INOpulse for PAH—Phase 2 Part A Trial Results for Patient Subgroups

Pulmonary Vascular Resistance

Parameter/Population		Placebo	Inhaled nitric oxide dose (mcg/kg ideal body weight/hour) 25	75
Total number of patients randomized		26	27	27
On LTOT	Number analyzed	10	15	19
	Baseline (mean)	580.1	605.2	614.9
	Change from Baseline (mean)	125.5	-47.1	-17.5
	p-value (ANOVA)	—	0.018	0.024
≥ 12 hours per day (Compliant)	Number analyzed	10	12	18
	Baseline (mean)	527.6	747.2	670.6
	Change from Baseline (mean)	146.5	-66.9	-5.1
	p-value (ANOVA)	—	0.023	0.027

Six-Minute Walk Distance

Parameter/Population		Placebo	Inhaled nitric oxide dose (mcg/kg ideal body weight/hour) 25	75
Total number of patients randomized		26	27	27
LTOT	Number analyzed	10	15	18
	Baseline (mean)	333.5	301.5	292.2
	Change from Baseline (mean)	-10.7	9.1	34.9
	p-value (ANOVA)	—	0.320	0.021
≥ 12 hours per day (Compliant)	Number analyzed	10	12	16
	Baseline (mean)	330.0	316.3	294.5
	Change from Baseline (mean)	-10.1	8.5	37.0
	p-value (ANOVA)	—	0.374	0.021

INOpulse was relatively well-tolerated in Part A of this trial. Our Independent Data Safety Monitoring Board evaluated the safety analysis from Part A of the trial in November 2014 and recommended proceeding with Part B of the trial. Drug-related serious adverse events, or SAEs, occurred in no patients in the placebo group and one subject in each of the 25 mcg and 75 mcg groups.

INOpulse—Phase 2 Part A Trial Results for All Patients: Summary Safety Data

		Inhaled nitric oxide dose (mcg/kg ideal body weight/hour)	
Number of Patients	**Placebo**	**25**	**75**
Number of Patients	26	27	27
Total Adverse Events (AEs)	23	22	26
Drug related AEs	9	10	9
Total Serious Adverse Events (SAEs)	4	4	9
Drug related SAEs	0	1	1
Deaths	1	0	0
Discontinuation due to AEs	1	1	2

One patient in the placebo arm died during Part A of the trial due to worsening PAH. SAEs were reported for four patients in the placebo arm, including one each of: pneumonia/worsening PAH, catheter-related infection, ascites and left hip sciatica. Each of these were assessed by the investigator for the trial as unrelated. Four patients in the 25 mcg low-dose active treatment arm experienced SAEs, including bacteremia, myelodysplastic syndrome, increased shortness of breath and dyspnea, one of which was assessed as possibly related to trial therapy. The 75 mcg high-dose active treatment arm had nine patients with SAEs. The most common SAEs reported in the 75 mcg group were syncope and bronchitis/tracheobronchitis, one of which was assessed as possibly related to trial therapy. Discontinuation of trial therapy due to adverse events, or AEs, occurred for two patients in the 75 mcg arm and one subject in each of the 25 mcg and placebo arms.

Pivotal Phase 3 Clinical Trials

We believe the results from Part A of our Phase 2 clinical trial provide sufficient indication of clinical benefit and safety to continue development of INOpulse for PAH in pivotal Phase 3 clinical trials. We had an End of Phase 2 meeting with the FDA on January 8, 2015. Based on this discussion, we plan to conduct this Phase 3 program as two adequate and well-controlled confirmatory trials, and we will conduct these two trials either sequentially or in parallel. In March 2015, we requested feedback on the proposed trial design from the Scientific Advice Working Party of the EMA. We currently intend to begin the Phase 3 program in the second half of 2015 and we estimate that, once initiated, each trial will take approximately three years to complete.

We expect one of the trials to have two arms—placebo and 75 mcg active dose—and the other to have three arms—placebo, 50 mcg active dose and 75 mcg active dose. Each arm is planned to have approximately 94 patients. Based on our discussions with the FDA, we expect that the primary endpoint of the trial will be change in six-minute walk distance evaluated at 18 weeks. In addition, we expect to have a secondary endpoint of time to clinical worsening, which we plan to analyze based on combined data from both trials to ensure adequate power for this assessment. We also plan to evaluate hemodynamic changes using right heart catheterization in a subset of patients.

We expect that enrollment for these trials will focus on patients with confirmed PAH who are treated with at least one approved PAH specific therapy and LTOT and who are willing to be compliant on therapy for at least 16 hours a day. We plan to conduct both trials with a two week run-in period, prior to the start of clinical dosing, to enrich enrollment for patients who show a high degree of adherence (i.e., an average of at least

16 hours of use per day) during this run-in period. We plan to use the Mark2 in these Phase 3 clinical trials. Results from our usability testing suggest that compliance with the Mark2 may be better than was the case with the first generation INOpulse DS device. We expect that the Phase 3 clinical trials will be multi-center multi-country trials with a focus on sites in North America and Europe.

We intend to finalize the clinical trial design following additional discussions with the FDA as well as with other regulatory authorities, including with the EMA.

INOpulse for PH-COPD

We are developing INOpulse for PH-COPD to address a significant unmet medical need that we believe is often overlooked in everyday clinical practice because of the lack of available therapy. Pulmonary hypertension is more prevalent among those COPD patients who have advanced loss of respiratory function and low peripheral blood oxygen levels requiring treatment with LTOT. The co-morbidity of pulmonary hypertension in these patients leads to cardiovascular complications from the added strain on the right ventricle of the heart. Current drug therapies for COPD are targeted to relieve the symptoms and complications of the respiratory component of the disease. Unlike these therapies, INOpulse is directed at treating the cardiovascular complications of PH-COPD. We believe PH-COPD patients on LTOT who are at risk for cardiovascular complications could benefit from use of INOpulse in addition to any respiratory benefits that result from their existing treatments.

Disease Background and Market Opportunity

COPD is a progressive disease caused by chronic inflammation and destruction of the airways and lung tissue. While COPD is primarily a respiratory disease, over time, as the disease progresses, the chronic pulmonary restrictions and resulting deprivation of adequate oxygen, or hypoxia, can contribute to vasoconstriction in the pulmonary arterial bed. In addition, COPD patients can have deficiency in endogenous nitric oxide production in their lungs, which can worsen vasoconstriction. This pulmonary vasoconstriction puts pressure on the right side of the heart, making it less able to cope with stressors and potentially leading to progressive cardiac dilation, heart failure and death. This cardiovascular component of COPD is, we believe, often overlooked despite pulmonologists' general awareness of the problem, in part because there are no specific therapies for the condition in these patients. While it is widely believed that the cardiovascular complications of COPD occur only in the advanced stage of the disease as a consequence of chronic hypoxemia, recent findings demonstrate an earlier involvement of the cardiovascular system in this disease.

In 2010, Datamonitor estimated that approximately 12 million patients in the United States were being treated for COPD and that over 1.4 million of these patients were being treated with LTOT. Based on academic studies, we estimate that 50% of COPD patients on LTOT in the United States have pulmonary hypertension. Even though the degree of pulmonary hypertension in these patients is milder than in PAH patients, data published in literature suggests that even small elevations in mean pulmonary artery pressure in patients with advanced COPD can impact hospitalization, patient-assessed functional outcomes and mortality. Pulmonary hypertension is a well-known predictor of increased morbidity and mortality in COPD patients and is associated with poor quality of life, worse clinical outcomes and shorter survival time. Based on a long-term study completed in 1992 and published in 1995, PH-COPD patients had a four-year survival rate of approximately 50%. By contrast, in this same long-term study, COPD patients with similar pulmonary functions, but without pulmonary hypertension, had a four-year survival rate of 80%.

We expect INOpulse for PH-COPD, if approved, would be a treated as a specialty drug. Specialty drugs are typically high-cost medications, often ranging in price in the United States from approximately $15,000 to $50,000 per patient per year, used to treat rare or complex conditions, requiring close clinical management and special handling and distributed through specialty pharmacies.

Scientific Rationale for Use of INOpulse for PH-COPD

The mechanism of action of inhaled nitric oxide in vasodilation at the alveolar smooth muscle in PH-COPD is similar to its action in PAH. Like endogenous pulmonary nitric oxide, inhaled nitric oxide works by selectively relaxing lung vascular smooth muscles, causing dilation of pulmonary blood vessels and consequently increased pulmonary blood flow. This reduces the elevated pulmonary artery pressure in patients with PH-COPD.

PH-COPD patients generally have hypoxemia as a result of deteriorating lung function, which can be treated with supplemental oxygen therapy. However, these patients are not treated with currently approved PAH-specific drugs because these drugs can worsen hypoxemia. This worsening can occur when these drugs, which are systemically bioavailable, cause indiscriminate pulmonary vasodilation, even in poorly ventilated alveoli, resulting in lower average blood oxygenation levels. We believe that inhaled nitric oxide, as a locally active selective pulmonary vasodilator with minimal systemic effects, can drop pulmonary arterial pressures, and when delivered with INOpulse as a targeted pulse to the well-ventilated alveoli, avoid this indiscriminate vasodilation and the consequent lowering of blood oxygen levels.

The targeted delivery of inhaled nitric oxide to specific alveoli is important because early trials with continuous-flow inhaled nitric oxide reduced pulmonary arterial pressure in PH-COPD patients but also resulted in lowering of blood oxygen levels. It was postulated that this unwanted effect might be avoided by administering nitric oxide as a brief pulse at the beginning of each breath because well-ventilated alveoli open faster, and a brief early pulse would only reach these alveoli. As early as 1997, this concept was demonstrated by testing inhaled nitric oxide in PH-COPD patients during exercise, which allowed the dose to mimic pulse dosing. Recently, data from a computational fluid-flow modeling study we conducted, using high resolution computed tomography scans and computer simulations, supported this hypothesis that early pulsed delivery of nitric oxide could be directed specifically to the well-ventilated alveoli.

Clinical Development Program

INOpulse for PH-COPD is designated as a drug-device combination by the FDA and is being evaluated through the Division of Cardiovascular and Renal Products of the Center for Drug Evaluation and Research with consultation from the Division of Pulmonary, Allergy, and Rheumatology Products and the Center for Devices and Radiological Health. In our IND for PH-COPD, we referenced all of the information in our IND for PAH and included data from a Phase 2 clinical trial that Ikaria commenced in 2005 but terminated due to lack of enrollment after one subject was treated. The one subject experienced a serious adverse event of hypoxia, which was deemed unrelated to treatment. The data referenced in our IND, as well as the years of use of the marketed product, demonstrate that nitric oxide is well tolerated. The FDA has agreed that the IND package is complete and adequate for supporting Phase 2 clinical development of INOpulse for PH-COPD. The FDA also agreed that no additional pre-clinical studies are needed to support product approval.

In the European Union, where there is no formal drug-device designation, we expect that INOpulse for PH-COPD will be evaluated by the EMA as a drug with specific reference in the label to the device and cannula, which will require a separate CE mark from a Notified Body.

In an initial three-month, open-label chronic-use Phase 2 trial, pulsed inhaled nitric oxide significantly reduced pulmonary arterial pressures in PH-COPD patients on LTOT and did so without causing hypoxemia, which is a significant concern for these patients. The inhaled nitric oxide was administered using a device that delivered pulsed nitric oxide as a fixed amount per breath along with the oxygen using a single lumen nasal cannula. This trial, completed in 2000, was conducted in two parts, an initial acute dose titration part and a three-month chronic ambulatory use part. In the initial acute test, each patient was treated with doses of 10, 15, 20, 25 and 30 ppm nitric oxide in a step-wise escalation from the lowest to higher doses. Each patient was assessed for drops in mean pulmonary arterial pressures, or mPAP, as well as for changes in oxygenation levels. The mean acute change in mPAP in this trial was a reduction of approximately 4 mmHg from a baseline of 27

mmHg across all doses. In another measure of the hemodynamic effects of the drug, the pulmonary arterial systolic pressure reduced by 2.7 to 3.6 mmHg across the nitric oxide doses tested. Based on the individual mPAP and oxygenation level changes in the acute test, each patient was assigned an individualized dose to be used in the second part of the trial which was a three-month evaluation. The patients were then randomized to either the control group for treatment with oxygen therapy or to the active group for treatment with both oxygen and the individually selected dose of nitric oxide over a period of three months. A total of 32 patients completed the three month portion per protocol, 15 of whom had been randomized to drug therapy and 17 of whom were randomized to the control group. At the end of the three month chronic use portion of the trial, patients in the nitric oxide arm had a statistically significant decrease from baseline in mPAP of 6.8 mmHg compared to an increase in mPAP of 0.9 mmHg in the oxygen alone control arm of the trial ($p < 0.001$) demonstrating a sustained and potentially strengthened effect of inhaled nitric oxide on mPAP over three months. In addition, at the three month evaluation, the patients treated with pulsed inhaled nitric oxide had no worsening of blood oxygen levels compared to the control group suggesting no worsening of oxygen exchange in the lungs.

In June 2012, this data was submitted to the FDA as part of the IND package for INOpulse for PH-COPD. Based on discussions with the FDA, we believe this trial is an adequate Phase 2 trial. The FDA has asked us to confirm the dose range and the safety related to hypoxemia in PH-COPD patients using the INOpulse device, prior to proceeding to large scale trials. Following this guidance, we conducted a Phase 2 acute dose ranging randomized placebo-controlled trial in 159 patients with the INOpulse DS device, with doses ranging from 3 mcg to 75 mcg. This Phase 2 trial, which we completed in July 2014, identified a dose range that showed similar efficacy versus baseline when compared to the initial acute effects of pulsed nitric oxide in the original chronic-use trial. The 10 mcg dose of INOpulse showed a decrease in pulmonary arterial systolic pressure from baseline of 5.4 mmHg ($p < 0.05$) and increasing the dose above 10 mcg did not result in a further decrease in pulmonary arterial systolic pressure from baseline indicating a plateau effect of the drug at 10 mcg and above. A post-hoc analysis of data combining all response data over the range of 10 mcg to 75 mcg showed a decrease in pulmonary arterial systolic pressure from baseline of 4.2 mmHg, which was significant and represented a mean decrease of approximately 9% from baseline. In addition, in our confirmatory trial, none of the INOpulse doses tested had an adverse effect on hypoxemia relative to placebo with a total of 48 patients with confirmed oxygenation level decrease greater than 5 mmHg from baseline (16/40 in placebo; 32/84 in inhaled nitric oxide). While the reduction in pulmonary arterial pressure did not reach statistical significance versus placebo in this acute setting, as the decrease in pulmonary arterial systolic pressure from baseline in the placebo group was 1.9 mmHg, we believe that the results have confirmed a dose range for this therapy that delivers a significant reduction in pulmonary arterial pressure versus baseline without causing hypoxemia in patients with PH-COPD.

We are currently designing a three-month Phase 2b trial to evaluate safety and efficacy for chronic use of INOpulse for PH-COPD. We plan to finalize the protocol following discussions with regulatory authorities in the United States and European Union. We currently intend to begin this Phase 2b trial in the second half of 2015 and, once initiated, we expect the trial will take approximately 18 months to complete.

INOpulse for Other Pulmonary Hypertension Conditions

Pulmonary hypertension disease is often classified according to the WHO classification system which groups patients with pulmonary hypertension according to the underlying etiologies, or causes, of the pulmonary hypertension. In this system, PAH is defined as Group 1 and PH-COPD is classified under Group 3, pulmonary hypertension due to lung disease and/or hypoxemia. We believe the mechanism of action of inhaled nitric oxide as a pulmonary vasodilator, and thus INOpulse, can be effective in treating pulmonary hypertension related to other conditions, including pulmonary hypertension associated with PH-IPF and other interstitial lung diseases, CTEPH and pulmonary hypertension associated with sarcoidosis.

While there are two recently approved treatments for IPF, there are currently no approved therapies for PH-IPF. In 2013, riociguat (Adempas) was the first drug therapy approved for treating CTEPH, although other PAH medications are sometimes used to treat this condition. Patients with sarcoidosis are often treated with

steroids or other anti-inflammatory medications, however, there are no therapies approved to treat the PH associated with this disease.

Our current license from Ikaria covers only the development of INOpulse for PAH, PH-COPD and PH-IPF. We would need to obtain additional license rights from Ikaria before beginning development of INOpulse for any other indication.

BCM for Prevention of Cardiac Remodeling Following a STEMI

We are developing BCM through the medical device regulatory pathway to prevent congestive heart failure following a STEMI, which is a type of severe heart attack. Patients who suffer a STEMI are at increased risk for congestive heart failure due to potential cardiac remodeling, which is a structural change in the size and shape of the heart that affects its ability to function normally. This change includes thinning of the left ventricle wall at the infarction and the adjacent border zone, outward bulging of the infarcted region, hypertrophy of the non-infarcted portion of the left ventricle and dilation of the left ventricle chamber. Cardiac remodeling increases mechanical stresses on the left ventricular wall and reduces the efficiency of pumping blood often leading to congestive heart failure.

BCM is intended to prevent cardiac remodeling by reducing the abnormal increase in ventricular wall stress and structural changes in the heart after a STEMI. Once blood flow has been re-established to the affected heart muscle of a patient following a STEMI, a physician deploys BCM through the coronary artery related to the infarcted region of the left ventricle. BCM is designed to flow into the damaged heart muscle where it forms a flexible scaffold to enhance the mechanical strength of the heart muscle during recovery and repair, thereby preventing cardiac remodeling. We have an exclusive worldwide license to BCM under a license agreement we entered into with BioLine in August 2009.

Disease Background and Market Opportunity

An AMI is generally a sudden event resulting from a blockage of one or more of the arteries supplying blood to the heart. This can cause the heart muscle to die or temporarily stop working. In some patients, particularly those with large areas of the heart affected by the AMI, the dead or stunned muscle in the infarcted area can start to degrade even if blood flow is subsequently restored.

Given recent advances in treating AMIs, patients do not typically die of the acute event, especially in developed countries with good hospital systems. Instead, post-AMI patients are at an increased risk of congestive heart failure that results from the loss of structural support where the tissue has died, leading to a change in the shape of the heart, or remodeling, excess blood being left in the heart after it beats and increased strain on the left ventricular wall. This left ventricular dysfunction is characterized by increased ventricular volume and decreased ejection fraction, which is the fraction of blood in the heart that is pumped out each time it contracts. The early impact of the heart attack on ejection fraction and left ventricular end-systolic volume is predictive of left ventricular function one year after the initial event. This deterioration in left ventricular function, which indicates adverse ventricular remodeling, can eventually cause the heart not to pump enough blood to the body, leading to congestive heart failure. In a large controlled study, worsening of ventricular measures was predictive of both mortality and heart failure.

Data from long-term third-party studies suggests that the five-year post-AMI rate of congestive heart failure or death is approximately 35% to 40%. In addition, based on data presented from the study conducted in Olmstead County, Minnesota, we estimate that the three-year post-AMI rate of congestive heart failure or mortality among patients who have had an AMI is approximately 30%. We are developing BCM to fill this unmet medical need by providing structural support of the heart muscle in the early days and months following an AMI, which is a critical period when the extracellular matrix is first degraded and then reconstituted as part of the heart's response to the injury and the time at which the heart is at high risk for remodeling. We expect that

deploying BCM will help prevent cardiac remodeling and possibly the progression to advanced stages of congestive heart failure.

According to hospital claims data and American Heart Association estimates, in 2014, the estimated incidence of AMI hospital admissions in the United States will be over 900,000. There are two classifications of AMI, STEMI and non-STEMI. While both types of AMIs can cause significant damage to the heart, STEMIs tend to have more severe acute symptoms. We estimate that nearly one-third of AMI hospital admissions in the United States were for STEMI. Additionally, according to a report published in the European Heart Journal in 2010, over one million people suffer from AMI in Europe, over half of whom have a STEMI. The costs of treating the consequences of AMI can be substantial. The American Heart Association reported that the total cost of congestive heart failure in 2012 was approximately $30.0 billion in the United States, and we estimate that approximately 40% of these patients were treated for congestive heart failure following an AMI. The average hospitalization costs in the United States for congestive heart failure have been estimated to be in the range $17,000 to $21,000 per admission with total lifetime medical costs following congestive heart failure diagnosis estimated at more than $100,000 per patient. Therefore, we believe BCM could be a treatment that would help to prevent cardiac remodeling and thereby reduce the incidence of congestive heart failure, which could generate significant medical cost savings in addition to improving the quality of life of these patients.

Scientific Rationale for Use of BCM in the Prevention of Cardiac Remodeling Following a STEMI

BCM is a clear, low-viscosity solution containing sodium alginate and calcium gluconate. Alginates, which are complex sugars obtained from seaweed, have been used extensively in the food industry as well as by the pharmaceutical and medical device industries. In medical devices, alginates have been used as wound dressings, as bone-void fillers and to create dental impressions. BCM's specific, patent-protected composition has been optimized to be partially cross-linked by calcium ions and to maintain a free-flowing liquid state for injection into the blood stream. However, when injected into the heart following an AMI, we believe that BCM will flow into the damaged heart muscle where it will come into contact with the additional extracellular calcium that is released by the newly dead heart muscle cells, resulting in the formation of additional cross-links within the alginate. These cross-links turn BCM into a gel meshwork with mechanical properties similar to the normal extracellular cardiac matrix. Based on data from animal studies, we believe these properties allow BCM to provide temporary structural support to the wall of the heart while it heals after an AMI.

Once deposited, BCM remains in the infarct zone for a few months. As the heart heals and the extracellular calcium levels return to normal, the crosslinks in the gel slowly degrade, and the alginate returns to liquid form and is excreted via the kidneys. In our pre-clinical animal studies of BCM, tissue sample analysis has shown that most of the alginate dissipates within three months and is no longer detectable in the heart or elsewhere in the body within six months after BCM injection. In an academic study published in the Journal of the American College of Cardiology, pigs were injected with either BCM or saline following an AMI. In this study, the pigs that received saline had approximately 44% greater enlargement in left ventricular chamber volume after 60 days compared to the pigs that received two milliliters of BCM. In another academic study conducted in dogs with AMI, deploying BCM at any time within one week of an AMI reduced cardiac remodeling compared to placebo.

Clinical Development Program

BCM is a Class III medical device that we are developing to prevent cardiac remodeling and subsequent congestive heart failure after AMI following successful re-opening of the blood vessels. We are currently conducting a clinical trial of BCM, which is designed as a CE mark registration trial in the European Union. We refer to this trial as our PRESERVATION I trial, and it is designed as a double-blind, placebo-controlled trial, and the primary endpoint is change in anatomical measurements six months after device deployment.

The principal treatment for a STEMI is to re-establish blood flow in the blocked coronary artery at the earliest possible opportunity. This can be achieved by percutaneous coronary intervention, dissolving the

blockage with medications or open heart surgery. BCM is designed to be deployed via a percutaneous coronary intervention into the previously blocked coronary artery after blood flow has been re-established.

We are developing BCM in the United States under an IDE and in consultation with a Notified Body in the European Union, which regulates the testing and use of devices. For our IDE application, we performed animal and *in vitro* studies and device effectiveness studies in pigs. Our pre-clinical studies demonstrated that BCM was well tolerated and showed activity in reducing cardiac remodeling after AMI in pigs when deployed in either a dedicated percutaneous coronary intervention procedure or during an initial percutaneous coronary intervention procedure. The FDA has agreed that the non-clinical package is complete and adequate for supporting clinical development, as specified in the IDE, and for registration of BCM.

The first human trial for BCM was a pilot clinical trial conducted by BioLine in Europe and completed in 2009, in which BCM was safely administered to 27 patients within seven days following a moderate to large STEMI and percutaneous coronary intervention. This open-label trial, in which all patients were treated with a two milliliter device, was conducted in multiple centers in Germany and Belgium and included patients who had experienced a first AMI of substantial size. The primary purpose of this trial was to evaluate the safety of BCM deployment. In addition, some efficacy parameters could be observed as all patients suffered a STEMI and had serial echocardiography studies performed at one, three and six months. A total of 27 patients (mean age 54±9 years) after a STEMI were treated during the course of this trial. Twenty-four patients were male, and 19 had experienced an anterior AMI with peak creatine kinase levels of 3183±1490 international units per liter. The time from symptom onset to primary percutaneous coronary intervention ranged from 0.6 to 84.7 hours (with a mean of 9.9±16.9 hours and a median of 3.8 hours). There were no serious adverse events observed with BCM at deployment. In this trial, eight patients experienced at least one treatment-emergent serious adverse event, and one event, a single episode of syncope that occurred 172 days after BCM deployment, was judged as possibly device related. In addition, 21 patients reported at least one adverse event in the initial six-month follow-up period. This data showed that BCM was well tolerated when deployed in patients following an AMI. In addition, standard echocardiogram measures of heart function were performed. In the six-month evaluation, patients in the trial, each of whom had large STEMIs, had measures of left ventricular function, including left ventricular end diastolic index, of left ventricular end systolic volume index and of left ventricular ejection fraction that indicated no change from baseline. Although interpretation of this data is limited by the lack of a control group, data from patients who were treated showed little change in these left ventricular measures, the worsening of which have been linked to mortality and heart failure.

In addition to the short-term testing during the first six months following the STEMI, the 27 patients had annual follow-up safety evaluations planned for up to five years. At the four-year follow-up evaluation, which is the most recent data set reported, 25 of the 27 patients were confirmed to still be alive. Of the two patients not confirmed alive, one died from T-cell lymphoma, which was likely a pre-existing condition, and one was lost to follow-up between the three- and four-year follow-up evaluations. However, the patient lost to follow-up had no device-related adverse events at the three-year follow-up evaluation. Of the 25 patients who were confirmed to be alive at year four, one had a hospitalization for congestive heart failure, which occurred within one year of device deployment. In addition, based on available data, during the four-year evaluation period, five patients experienced at least one cardiac ischemic event (nine cardiac ischemic events in total), none of which were considered to be related to BCM. This data from the four-year safety follow-up evaluations is better than we expected based on our review of publicly reported data from two long-term third-party studies of AMI patients, the Framingham Heart Study and the Olmstead County study. The data from these two studies suggest that the rate of congestive heart failure or death five years following an AMI is approximately 35% to 40%. In addition, based on data presented from the Olmstead County study, we estimate that the three-year post-AMI rate of congestive heart failure or mortality among patients who have had an AMI is approximately 30%.

Our ongoing PRESERVATION I trial is a CE mark registration trial for EU regulatory purposes and is comparable to a feasibility clinical trial in the United States. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure at almost 90 clinical sites in Europe, Australia, North America and Israel. Our key inclusion criteria for this trial include that patients must have:

- suffered from a large STEMI as measured by cardiac enzymes;
- clinical signs of significant cardiac damage;
- imaging evidence of impaired heart function; and
- had a primary percutaneous coronary intervention with a stent placed.

In this double-blind trial, patients are randomized in a two-to-one ratio to BCM or placebo. The trial device is injected in a second percutaneous coronary intervention two to five days after the initial myocardial infarction. The primary endpoint is change in the anatomical measurement of left ventricular end-diastolic volume index by echocardiography measured six months after device deployment. Secondary endpoints include the measurement of functional capacity of change in six-minute walk distance and the measurement of patient reported outcome as recorded on the quality of life tool of Kansas City Cardiomyopathy Questionnaire. Other endpoints include a measurement of BCM in the peripheral circulation as an assessment of the pharmacokinetics of BCM, electrocardiogram measures and other anatomic endpoints, including change in left ventricular end-systolic volume index and ejection fraction. In addition, as required by the trial protocol, we will follow all patients to monitor safety for a period of five years after device deployment. The Data Safety Monitoring Board for this trial has met six times to evaluate the safety data and on each occasion has approved the continuation of the trial as planned. We expect to report top line results from this trial in mid-2015. We also expect that if our PRESERVATION I trial is successful, we will rely on the results to seek CE marking for BCM in the European Union potentially in the first half of 2016.

Assuming positive results from our PRESERVATION I trial, we plan to conduct a second, larger clinical trial to support approval in the United States through the PMA pathway. We met with the FDA to discuss U.S. regulatory requirements for a pivotal clinical trial. Based on discussions with the FDA Center for Devices and Radiological Health in May 2010, we expect that our pivotal trial will include approximately 1,000 patients, having a composite endpoint of anatomic measurements of left ventricular end-diastolic volume index or ejection fraction, a patient outcomes measurement test and a functional measure such as six-minute walk distance or a cardiopulmonary stress test. We currently expect to begin this trial in the first half of 2016, and we estimate that, once initiated, the trial will take approximately two to three years to complete.

If the PRESERVATION I trial demonstrates that BCM is well tolerated and has a clinical benefit in severe STEMIs when deployed in a second percutaneous coronary intervention procedure, we intend to consider testing BCM in an expanded population, including patients with moderate STEMIs, and for deployment of BCM during the primary percutaneous coronary intervention procedure, eliminating the need for a second invasive procedure. We are currently designing a trial to evaluate the safety of deploying BCM in the primary percutaneous coronary intervention procedure after a large STEMI. The secondary objective of this trial will be to evaluate the efficacy of BCM six months after deployment using ventricular remodeling measures. We currently intend to begin this trial in the second half of 2015, assuming successful completion of PRESERVATION I, and we expect the trial will take approximately one year to complete.

Relationship with Ikaria after the Spin-Out

The development of our programs was initiated under the leadership of our scientific and development team while at Ikaria. Ikaria's lead product, INOmax, is an inhaled nitric oxide product used for treatment of persistent pulmonary hypertension of the newborn. Our understanding of the medical applications of nitric oxide and associated delivery devices, as well as our innovative approach to the pulsed delivery of nitric oxide, originated at Ikaria, and we in-licensed BCM while we were a part of Ikaria.

In October 2013, Ikaria completed an internal reorganization of certain assets and subsidiaries, in which it transferred to us exclusive worldwide rights, with no royalty obligations, to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF. Following the internal reorganization, in February 2014, Ikaria

distributed all of our then outstanding units to its stockholders through the payment of a special dividend on a pro rata basis based on each stockholder's ownership of Ikaria capital stock. We refer to Ikaria's distribution of our then outstanding units to its stockholders as the Spin-Out.

Shortly after the Spin-Out, Ikaria was acquired by entities affiliated with Madison Dearborn Partners. On March 5, 2015, Mallinckrodt plc, or Mallinckrodt, and Ikaria announced that they had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria. Mallinckrodt and Ikaria have announced that they expect this transaction to be completed in the second calendar quarter of 2015.

Ikaria retains the right to develop and commercialize inhaled nitric oxide products, including pulsed products, in all indications other than PAH, PH-COPD and PH-IPF.

In connection with the Spin-Out, we entered into several agreements with Ikaria providing for, among other things, the provision of transition services, the cross license of certain intellectual property, commitments not to compete, the manufacture and supply of the INOpulse drug and device and certain employee matters.

Transition Services Agreement

In February 2014, we entered into a transition services agreement with Ikaria, which we refer to as the TSA. Pursuant to the terms and conditions of the TSA, Ikaria has agreed to use commercially reasonable efforts to provide certain services to us, including human resources support, real estate support, information technology support, accounting and tax support, treasury support, financial planning and analysis support, purchasing support, management/executive services, legal services, quality services, regulatory services, drug and device safety services, business development support, biometrics support and manufacturing support. Ikaria is obligated, subject to the terms of the TSA (including the early termination provisions thereof and our obligation to use commercially reasonable efforts to provide the services for ourselves as soon as practicable), to provide such services until February 2016.

Ikaria has also agreed, on the terms and subject to the conditions of the TSA, to use commercially reasonable efforts to allow our employees to remain in Ikaria's Hampton, New Jersey facility for the continued operation of our business during the term of the TSA.

We are obligated to pay Ikaria a service fee in the amount of $772,000 per month and to reimburse Ikaria for any out-of-pocket expenses incurred in connection with its provisions of services under the TSA, any taxes imposed on Ikaria in connection with the performance or delivery of services under the TSA and any costs and expenses incurred by Ikaria in connection with the performance of any services that require resources outside of the existing resources of Ikaria or that otherwise interfere with the ordinary operations of Ikaria's business. This monthly service fee is be payable by us regardless of the frequency or quantity of services actually utilized by us under the TSA, and our obligation to pay such monthly service fee until February 2016 will survive any early termination of the TSA. At the time we entered into the TSA, we also entered into an escrow agreement, pursuant to which we deposited $18.5 million, representing the aggregate amount of the monthly service fees payable by us under the TSA, into escrow to guarantee our payment of such fees to Ikaria. We are also obligated to pay any fees, costs, expenses or other amounts incurred by Ikaria to obtain the right to allow our employees to remain in the Hampton, New Jersey facility during the term of the TSA.

Exclusive Cross-License, Technology Transfer and Regulatory Matters Agreement

In February 2014, we entered into an exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria. Pursuant to the terms of the license agreement, Ikaria granted to us a fully paid-up, non-royalty bearing, exclusive license under specified intellectual property rights controlled by Ikaria to engage in the development, manufacture and commercialization of nitric oxide, devices to deliver nitric oxide and related services for or in connection with out-patient, chronic treatment of patients with PAH, PH-COPD or PH-IPF, which we refer to collectively as the Bellerophon indications.

We have granted to Ikaria a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights that we control to engage in the development, manufacture and commercialization of products and services for or used in connection with the diagnosis, prevention or treatment, whether in- or out-patient, of certain conditions and diseases other than the Bellerophon indications and for the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital, which we refer to collectively as the Ikaria nitric oxide business.

We have agreed that, during the term of the license agreement, we will not, without the prior written consent of Ikaria, grant a sublicense under any of the intellectual property licensed to us under the license agreement to any of our affiliates or any third party, in either case that directly or indirectly competes with the Ikaria nitric oxide business. We have also agreed that we will include certain restrictions in our agreements with customers of our products to ensure that such products will only be used for the Bellerophon indications.

The license agreement will expire on a product-by-product basis for products for a specific Bellerophon indication at such time as we are no longer developing or commercializing any product for such indication. The license agreement may be terminated by either party in the event an act or order of a court or governmental authority prohibits either party from substantially performing under the license agreement. Either party may also terminate the license agreement in the event of an uncured material breach by the other party or in the event the other party is insolvent or in bankruptcy proceedings. Ikaria may also terminate the license agreement if we or any of our affiliates breach the agreements not to compete described below, or if we or any successor to our rights under the license agreement markets a generic nitric oxide product that is competitive with INOmax. Under certain circumstances, if the license agreement is terminated, the licenses granted to Ikaria by us will survive such termination.

Agreements Not to Compete

In September 2013, October 2013 and February 2014, we and each of our subsidiaries entered into an agreement not to compete with Ikaria. We refer to these agreements collectively as the agreements not to compete. Pursuant to the agreements not to compete, we and each of our subsidiaries agreed not to engage, anywhere in the world, in any manner, directly or indirectly, until the earlier of five years after the effective date of such agreement not to compete or the date on which Ikaria and all of its subsidiaries are no longer engaged in such business, in:

- the development, manufacture, commercialization, promotion, sale, import, export, servicing, repair, training, storage, distribution, transportation, licensing or other handling or disposition of any product or service (including, without limitation, any product or service that utilizes, contains or includes nitric oxide for inhalation, a device intended to deliver nitric oxide or a service that delivers or supports the delivery of nitric oxide), bundled or unbundled, for or used in connection with (a) the diagnosis, prevention or treatment, in both adult and/or pediatric populations, and whether in- or out-patient, of: (i) hypoxic respiratory failure associated with pulmonary hypertension, (ii) pulmonary hypertensive episodes and right heart failure associated with cardiovascular surgery, (iii) bronchopulmonary dysplasia, (iv) the management of ventilation-perfusion mismatch in acute lung injury, (v) the management of ventilation-perfusion mismatch in acute respiratory distress syndrome, (vi) the management of pulmonary hypertension episodes and right heart failure in congestive heart failure, (vii) pulmonary edema from high altitude sickness, (viii) the management of pulmonary hypertension episodes and right heart failure in pulmonary or cardiac surgery, (ix) the management of pulmonary hypertension episodes and right heart failure in organ transplant, (x) sickle cell vaso-occlusive crisis, (xi) hypoxia associated with pneumonia or (xii) ischemia-reperfusion injury or (b) the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital; or

- any and all development, manufacture, commercialization, promotion, sale, import, export, storage, distribution, transportation, licensing, or other handling or disposition of any terlipressin or any

other product within the pressin family, (a) intended to treat (i) hepatorenal syndrome in any form, (ii) bleeding esophageal varices or (iii) septic shock or (b) for or in connection with the management of low blood pressure.

The agreements not to compete expressly exclude the Bellerophon indications.

In February 2014, we also entered into drug and device clinical supply agreements and an employee matters agreement with Ikaria See "Manufacturing" below for a description of the drug and device clinical supply agreements and "Certain Relationships and Related Person Transactions—Relationship with Ikaria" for a description of the employee matters agreement.

BioLine License Agreement

In August 2009, we entered into a license agreement with BioLineRx Ltd. and BioLine Innovations Jerusalem L.P., under which we obtained an exclusive worldwide license to BCM. Under the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize at least one product containing BCM. We have established a joint development committee with BioLine to oversee the development of BCM.

We paid BioLine a $7.0 million upfront payment in 2009 and a $10.0 million milestone payment in 2010. Under the terms of the license agreement, if we achieve certain clinical and regulatory events specified in the license agreement, we will be obligated to pay milestone payments to BioLine that could total, in the aggregate, up to $115.5 million, and if we achieve certain commercialization targets specified in the license agreement, we will be obligated to pay additional milestone payments to BioLine that could total, in the aggregate, up to $150.0 million. In addition, we will be obligated to pay BioLine a specified percentage of any upfront consideration we receive for sublicensing BCM, as well as royalties on net sales, if any, at a percentage ranging from 11% to 15%, depending on net sales level, of any approved product containing BCM, subject to offsets for specified payments to third parties made in connection with BCM. Our obligation to pay BioLine royalties will expire on a product-by-product and country-by-country basis on the date on which BCM is no longer covered by a valid claim in the licensed patent rights in the given country.

BioLine has the option, exercisable under specified circumstances, to manufacture any product containing BCM for us pursuant to terms to be negotiated by the parties. If BioLine exercises this option, we would generally be obligated to purchase at least a specified percentage of our BCM requirements from BioLine at a price calculated using a pre-agreed methodology, and the parties would be required to establish a joint manufacturing committee to coordinate manufacturing efforts.

Except under specified circumstances, neither we, nor any other person that controls, is controlled by, or is under common control with us, may directly or indirectly acquire more than a specified percentage of the equity or debt securities of BioLine, or urge, induce, entice or solicit any other party to acquire such securities, without BioLine's consent.

We and BioLine have the right to terminate the license agreement for an uncured material breach by the other party. In addition, we have the right to terminate the license agreement if at any time we determine that further development of products containing BCM is not warranted.

Manufacturing

INOpulse Drug Product

In February 2014, we entered into a drug clinical supply agreement with Ikaria, or the drug supply agreement, pursuant to which Ikaria has agreed to use commercially reasonable efforts to manufacture and supply, and we have agreed to acquire from Ikaria, our requirements for nitric oxide for inhalation and

corresponding placebo for use in our clinical programs for PAH, PH-COPD and PH-IPF. Pursuant to the drug supply agreement, we will pay to Ikaria an amount equal to Ikaria's internal and external manufacturing cost plus 20%. Under the terms of the drug supply agreement, we have also granted Ikaria a right of first negotiation in the event that we desire to obtain supply of nitric oxide for inhalation and corresponding placebo (or any variant thereof or any version with different specifications) for commercial use. The drug supply agreement will expire on a product-by-product basis on the date we discontinue clinical development of such product. In addition, either party may terminate the drug supply agreement in the event of an uncured material breach by the other party.

Ikaria manufactures pharmaceutical-grade nitric oxide at its facility in Port Allen, Louisiana. This facility, which we believe is operated in compliance with current Good Manufacturing Practices, or cGMP, is the only FDA-inspected site for manufacturing pharmaceutical-grade nitric oxide in the world. The primary manufacturing activity at the site is the commercial production of INOmax and production of INOpulse. This production includes the chemical synthesis of high-purity nitric oxide, which is the active pharmaceutical ingredient in INOmax and INOpulse, and the filling of the gas cylinders in which the products are packaged.

To support business outside of the United States, the Port Allen manufacturing facility has also successfully passed inspections by local agencies, the EMA, Health Canada; the Pharmaceutical and Medical Devices Agency, or PMDA, of Japan, and the Korean FDA, or KFDA. The EMA, the Health Protection Branch of Health Canada, PMDA and KFDA operate in a similar fashion to the FDA in that each requires submission of a dossier containing substantial evidence of safety and effectiveness prior to approval. These agencies' monitoring of safety in a post-marketing setting also is similar to that of the FDA.

The operations that Ikaria currently performs for us consist of two steps. The first step is to manufacture the concentrated drug product, which Ikaria conducts using the same processes that it uses to manufacture its own drug product. The second step is the filling operation in which the pre-mix product is mixed to the appropriate concentration and filled into the final cartridges that we use with INOpulse. As we have reduced the size and weight of INOpulse, we have also developed a smaller, more-concentrated drug cartridge for INOpulse. The filling process has been developed by Ikaria as a high-throughput batch fill process that leverages several technologies that Ikaria has developed, and we have licensed, to fill smaller containers at a higher pressure and purity and at a significantly higher production rate than prior technology.

This manufacturing system is designed to be modular and can be expanded as needed. The current installed capacity within the Port Allen plant is sufficient to support our INOpulse clinical program as currently planned. In addition, the plant has the capacity to expand to meet additional demand. We have a license from Ikaria to use this fill process technology to work with additional companies, as needed, to produce the final cartridge. Commercial supply manufacturing can be supported with additional units installed at the Port Allen site or other regional locations, by Ikaria or other manufacturers, as determined by distribution requirements. For our clinical trials, Ikaria can supply and ship product from the Port Allen site and the current cartridges are expected to have a shelf life of at least one year. We are testing the finished product to potentially establish a shelf life of up to two years.

INOpulse Drug Delivery Systems

Ikaria has a drug delivery system manufacturing facility in Madison, Wisconsin, at which it designs, engineers, assembles, packages and distributes drug delivery systems, including INOpulse. We entered into a services agreement with Ikaria, effective as of January 1, 2015, which expires in February 2016, under which, among other things, Ikaria agreed to use commercially reasonable efforts to provide us with certain INOpulse device related services, including services related to device remediation, upgrades and refurbishment. In February 2015, we entered into an agreement with Flextronics Medical Sales and Marketing Ltd., a subsidiary of Flextronics International Ltd., or Flextronics, to manufacture and service the Mark2 devices that we expect to use in future clinical trials of INOpulse for PAH and INOpulse for PH-COPD.

Each version of our INOpulse device currently under development will be pre-programmed at the time of manufacture to the dose setting specified for the applicable indication. Since PAH patients have the potential for rebound pulmonary hypertension, which is a sudden and serious increase in pulmonary arterial pressure that results from therapy withdrawal, patients with this condition are required to have a backup system. Accordingly, we will be required to provide PAH patients with either a separate backup device or a device with a built-in pneumatic, or non-electrical, backup system. Also, pursuant to the terms of our license agreement with Ikaria, we are required to lease and not to sell our INOpulse devices as well as to track and maintain control of the indications for which each are used. We intend to meet these requirements by maintaining close monitoring of the use of the devices, including through planned remote data downloads and a system diagnostic feature.

BCM Product

We currently outsource the manufacture of BCM for use in clinical trials. BCM is manufactured by a third-party under the terms of a manufacturing and supply agreement which expires in April 2017. We plan to enter into a manufacturing and supply agreement for BCM with a third-party prior to April 2017.

BCM is composed of ultra-pure sodium alginate and calcium-D-gluconate. We purchase sodium alginate from FMC BioPolymer AS (doing business as NovaMatrix™) under the terms of a clinical supply agreement that expires in December 2018. We and FMC BioPolymer have agreed to negotiate a commercial supply agreement prior to the December 2018 expiration of the clinical supply agreement. Calcium-D-gluconate is a commodity item available from multiple suppliers. If BCM is approved for commercial sale, we will likely continue to outsource its manufacture to contract manufacturers.

BioLine has the option, exercisable under specified circumstances, to manufacture any product containing BCM for us pursuant to terms to be negotiated by the parties. If BioLine exercises this option, we would generally be obligated to purchase at least a specified percentage of our BCM requirements from BioLine at a price calculated using a pre-agreed methodology, and the parties would be required to establish a joint manufacturing committee to coordinate manufacturing efforts.

Competition

The biotechnology and pharmaceutical industries are highly competitive. There are many pharmaceutical companies, biotechnology companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our products. In addition, other companies are increasingly looking at cardiac and cardiopulmonary indications as a potential opportunity. It is possible that the number of companies seeking to develop products and therapies for the treatment of unmet needs in our target markets will increase.

Our competitors, either alone or with their strategic partners, may have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining approval for therapies and achieving widespread market acceptance. We anticipate that we will face intense and increasing competition as new drugs and advanced technologies become available.

Currently, there are 12 drugs approved for the treatment of PAH, within the following categories: prostacyclin and prostacyclin analogs (including Flolan (epoprostenol), which is marketed by GlaxoSmithKline, Tyvaso (treprostinil), Orenitram (treprostinil) and Remodulin (treprostinil), which are marketed by United Therapeutics Corporation, and Ventavis (iloprost) and Veletri (epoprostenol), which are marketed by Actelion Pharmaceuticals US, Inc., or Actelion), phosphodiesterase type-5 inhibitors (including Adcirca (tadalafil), which is marketed by United Therapeutics Corporation, and Revatio (sildenafil), which is marketed by Pfizer Inc.), endothelin receptor antagonists (including Letairis (ambrisentan), which is marketed by Gilead Sciences, Inc., and Opsumit (macitentan) and Tracleer (bosentan), which are marketed by Actelion) and a soluble guanylate

cyclase stimulator (Adempas (riociguat), which is marketed by Bayer HealthCare Pharmaceuticals Inc.). Actelion recently submitted an NDA to the FDA for selexipag, a selective prostacyclin receptor agonist.

There are also other treatments in Phase 1 and Phase 2 clinical development, including other nitric oxide generation and delivery systems, including GeNOsyl™, which is being developed by GeNO LLC, and a nebulized formulation of nitrite, which is being developed by Mast Therapeutics.

Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant, and we are not aware of any therapies for PH-COPD in advanced clinical development.

There are no generally accepted products approved for structural support to prevent cardiac remodeling following an AMI. Other product candidates that are currently in clinical development include stem cell therapies to restore heart muscle cells following an AMI, with large Phase 3 trials expected to be completed in 2018 or 2019. We do not expect BCM to compete with, or replace, current treatments for congestive heart failure following AMI, but instead believe it will become part of the treatment regimen used in conjunction with other therapies. In addition, because BCM can be delivered by a minimally invasive percutaneous coronary intervention procedure, we do not believe it will directly compete with devices that are used to treat congestive heart failure, which are designed for administration during open heart surgery or by intra-cardiac injection involving a thoracotomy procedure. These include: mesh restraining devices, for example HeartNet™; injectable biopolymers, for example Algisyl-LVR™; and implantable electro-stimulation devices, for example, CardioFit™. In addition, volume reduction surgery or cardiac assist devices, or pumps, are sometimes used to treat patients with congestive heart failure.

Patents and Proprietary Rights

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to protect, for example, our product candidates, related technologies and/or other aspects of the inventions that are important to our business. Our owned and licensed patents and patent applications cover patentable subject matter from composition of matter, methods of use, manufacturing processes for BCM and method of administration, devices and device components, critical safety features and design components with respect to INOpulse. However, patent protection is not available for the composition of matter of the active pharmaceutical ingredients in INOpulse since nitric oxide is a naturally occurring molecule.

Actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country. We also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

We plan to continue to expand our intellectual property estate by filing patent applications directed to inventions which provide additional patent protection for our product offering, for instance, device enhancements, safety features and manufacturing processes. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; maintain our licenses to use intellectual property owned by third parties; preserve the confidentiality of our trade secrets; and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also consider know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary positions.

A third party may hold intellectual property, including patent rights that are important or necessary to the development of our programs. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to obtain a license

from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially. For example, if we want to expand the indications for which we could develop and commercialize pulsed nitric oxide beyond PAH, PH-COPD and PH-IPF, we will need to obtain a license from Ikaria.

The patent positions of therapeutics companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions permit third parties to challenge issued patents in administrative proceedings which may result in further narrowing or even cancellation of patent claims. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors. Any patents that we own or license may be challenged, narrowed, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings declared by the U.S. Patent and Trademark Office, or USPTO, to determine priority of inventions for any patent applications filed with the USPTO on or before March 15, 2013. Likewise, derivation proceedings may also be declared for any patent filings filed after March 15, 2013.

The patents and patent applications that relate to our programs are described below.

INOpulse

As of March 25, 2015, we hold exclusive licenses from Ikaria to at least 80 patents and pending patent applications in both the United States and foreign countries including Australia, Brazil, Canada, China, Europe, Hong Kong, India, Indonesia, Israel, Japan, Korea, Mexico, the Philippines, Russia and Singapore. Certain of these issued patents and patent applications, if issued, will expire as late as 2033. These patent rights have been exclusively licensed for the treatment of patients with PAH, PH-COPD and PH-IPF and cover methods of delivery and the drug delivery device, as well as important safety features and the ornamental design of the drug delivery device.

A primary basis for patent exclusivity is based on pending and issued in-licensed patents directed to proprietary methods of administering pulsed inhaled nitric oxide, as well as a device for delivering the same. This patent family expires as late as 2027 in the United States and as late as 2026 in Australia, Brazil, Canada, China, Europe, Hong Kong, Japan and Mexico.

Another important basis for patent exclusivity is based on an in-licensed portfolio of one issued U.S. patent, three pending U.S. patent applications, and two Patent Cooperation Treaty pending patent applications, in each case directed to novel nasal cannula features that we believe are necessary for the accurate, safe and efficacious administration of pulsed nitric oxide. Each of these patents and patent applications, if issued, will expire in 2033 in the United States and abroad.

Another in-licensed patent family relates to features of the drug delivery canister necessary for providing drug product for use with our proprietary pulsing drug delivery device. This patent family includes one issued U.S. patent, one issued Japanese patent, one issued Mexican patent, one issued Singaporean patent and three issued Australian patents, as well as 16 pending patent applications in the United States, Brazil, Canada, China, Europe, Hong Kong, India, Indonesia, Israel, Japan, Korea, Mexico, the Philippines, Russia and Singapore. These pending applications, if issued, will expire in 2029, as well will the issued Australian, Japanese, Mexican and Singaporean patents. The issued U.S. patent will expire in 2030.

Several other patent families directed to device and safety features are pending. Furthermore, a design patent covering the ornamental design of the intended commercial device has been granted, and a design patent application is pending for the ornamental design of the clinical device.

In addition, the FDA has granted orphan drug designation to our nitric oxide program for the treatment of PAH, which could result in marketing exclusivity of seven years in the United States should this be the first NDA approved for inhaled nitric oxide in this indication. The active ingredient, nitric oxide, was previously approved by the FDA as a drug in a separate clinical application. Accordingly, any related patent rights will not be eligible for a patent term extension under relevant provisions of the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act.

BCM

Patent protection of BCM in the United States and in Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea and Mexico is provided by issued composition of matter and method of treatment patents and patent pending applications, which we in-license from BioLine, that cover the intended commercial product. These issued patents are not limited to treatment of cardiac tissue, affording broad protection for the use of BCM in treating any damaged body tissue. We were notified by the European Patent Office in July 2014 and October 2014 that Notices of Opposition to two European patents that we licensed from BioLine, one of which covers the BCM intended commercial product described above, have been filed with the European Patent Office. A Notice of Opposition initiates a process during which the European Patent Office can decide to reconsider an issued patent and modify or revoke some or all of the patent claims. We have the right to respond to the Notices of Opposition before the European Patent Office makes a decision whether or not any or all of the patent claims are to be modified or revoked. We filed a response to the first patent opposition in December 2014, and we filed a response to the second patent opposition in March 2015, as we believe the two issued patents were properly examined and appropriately granted by the European Patent Office. Furthermore, we believe the arguments made in the Notices of Opposition misstate the facts and lack scientific merit.

BCM will be regulated as a device and therefore data exclusivity will not be available. However, under the Hatch-Waxman Act, one issued U.S. patent covering the product will be eligible for patent term extension of up to five years to recover patent term lost during clinical trials. Accordingly, if the U.S. composition of matter patent that expires in 2029 is selected for this extension and a patent term extension is granted, certain rights under the patent may not expire until 2032 to 2034, depending on the timing of marketing approval and other factors. Corresponding issued patents in other countries will expire in 2024 and may also be eligible for patent term extensions. We do not expect to be granted a patent term extension for composition of matter patents in Europe, but patent term extensions may be available in other countries such as Japan and Israel.

Method of manufacturing patents that we have in-licensed have issued in the United States, Australia, China, Europe, India, Israel, Korea and Mexico and are pending in Canada. The U.S. issued patent expires in 2025 and the non-U.S. issued patents expire in 2024. The method of manufacturing patent applications we developed and own, if issued, will expire in the United States, Canada and Europe in 2032, not including any applicable patent term adjustment. Further, there is no abbreviated clinical trial pathway, such as an abbreviated new drug application, or ANDA, or a 505(b)(2) new drug application, for a device product approved via a PMA pathway.

Patent Term

The base term of a U.S. patent is 20 years from the filing date of the earliest-filed non-provisional patent application from which the patent claims priority. The term of a U.S. patent can be lengthened by patent term adjustment, which compensates the owner of the patent for administrative delays at the USPTO. In some cases, the term of a U.S. patent is shortened by terminal disclaimer that reduces its term to that of an earlier-expiring patent.

The term of a U.S. patent may be eligible for patent term extension under the Hatch-Waxman Act to account for at least some of the time the drug or device is under development and regulatory review after the patent is granted. With regard to a drug or device for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of the term of one U.S. patent. Thus, patent term extension is not available for INOpulse since the active moiety is nitric oxide, which is already subject to an approved NDA. The extended patent term cannot exceed the shorter of five years beyond the non-extended expiration of the patent or 14 years from the date of the FDA approval of the drug or device. Some foreign jurisdictions have analogous patent term extension provisions that allow for extension of the term of a patent that covers a device approved by the applicable foreign regulatory agency. In the future, if and when BCM receives FDA approval, we expect to apply for a patent term extension on the patent covering BCM that we believe will provide the best exclusivity position if extended.

Trade Secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. We typically rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. For example, elements of the manufacture of our products are based on trade secrets and know-how that are not publicly disclosed. We protect trade secrets and know-how by establishing confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. These agreements provide that all confidential information developed or made known during the course of an individual or entity's relationship with us must be kept confidential during and after the relationship. These agreements also provide that all inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary technology by third parties.

Trademarks

We also seek trademark protection where available and when appropriate. The symbol ™ indicates a common law trademark. Other service marks, trademarks and trade names appearing in this Annual Report on Form 10-K are the property of their respective owners.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, quality control, clearance, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products and medical devices. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drugs under the Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product

recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States. An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of pre-clinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of an NDA;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including Risk Evaluation and Mitigation Strategies, or REMS, and post-approval studies required by the FDA.

Pre-Clinical Studies

Pre-clinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as *in vitro* and animal studies to assess the safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of pre-clinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the pre-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, are submitted to the FDA as part of an IND.

Companies usually must complete some long-term pre-clinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Human Clinical Studies in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written study protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence.

In addition, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA or IND so long as the clinical trial is conducted in compliance with GCP, and the FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into a small number of healthy human subjects or patients with the target disease (e.g., cancer) or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- Phase 3: Phase 3 clinical trials are commonly referred to as “pivotal” studies, which typically denotes a study which presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug. In Phase 3 clinical trials, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical

trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant may eliminate the need to conduct certain pre-clinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Submission of an NDA to the FDA

NDAs for most new drug products are based on two full clinical studies that must contain substantial evidence of the safety and efficacy of the proposed new product. Assuming successful completion of required clinical testing and other requirements, the results of the pre-clinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, currently exceeding $2.1 million, and the sponsor of an approved NDA is also subject to annual product and establishment user fees, currently exceeding $104,000 per product and $554,000 per establishment. These fees are typically increased annually.

The FDA conducts a preliminary review of an NDA within 60 days of its receipt and informs the sponsor by the 74th day after the FDA's receipt of the submission whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process may be extended by the FDA for various reasons, including for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections cover all facilities associated with an NDA submission,

including drug component manufacturing (such as Active Pharmaceutical Ingredients), finished drug product manufacturing, and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The FDA may refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a drug for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA

will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions which can materially affect the potential market and profitability of the product. In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an ANDA to the agency. In support of such applications, a generic manufacturer may rely on the pre-clinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug.

Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or

bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicate that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

Orphan Designation and Exclusivity

Under the Orphan Drug Act, FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition (generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product). A company must request orphan product designation before submitting a NDA. If the request is granted, FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status receives the first FDA approval for the disease or condition for which it has such designation, the product will be entitled to orphan product exclusivity. Orphan product exclusivity means that FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a

different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, a NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. With enactment of the Food and Drug Administration Safety and Innovation Act, or FDASIA, in 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product or medical device may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a new drug product or a Class III medical device is typically one-half the time between the date a clinical investigation on human beings is begun and the submission date of an application for premarket approval of the product or medical device, plus the time between the submission date of an application for approval of the product or medical device and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product or medical device is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs or medical devices for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Review and Approval of Medical Devices in the United States

Medical devices in the United States are strictly regulated by the FDA. Under the FDCA a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or

other similar or related article, including a component, part or accessory which is, among other things: intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes. This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. If not, it is generally a medical device.

Unless an exemption applies, a new medical device may not be marketed in the United States unless and until it has been cleared through filing of a 510(k) premarket notification, or 510(k), or approved by the FDA pursuant to a PMA. The information that must be submitted to the FDA in order to obtain clearance or approval to market a new medical device varies depending on how the medical device is classified by the FDA. Medical devices are classified into one of three classes on the basis of the controls deemed by the FDA to be necessary to reasonably ensure their safety and effectiveness.

Class I devices are those low risk devices for which reasonable assurance of safety and effectiveness can be provided by adherence to the FDA's general controls for medical devices, which include applicable portions of the FDA's Quality System Regulation, or QSR, facility registration and product listing, reporting of adverse medical events and malfunctions and appropriate, truthful and non-misleading labeling, advertising and promotional materials. Many Class I devices are exempt from premarket regulation; however, some Class I devices require premarket clearance by the FDA through the 510(k) premarket notification process.

Class II devices are moderate risk devices and are subject to the FDA's general controls, and any other special controls, such as performance standards, post-market surveillance, and FDA guidelines, deemed necessary by the FDA to provide reasonable assurance of the devices' safety and effectiveness. Premarket review and clearance by the FDA for Class II devices are accomplished through the 510(k) premarket notification procedure, although some Class II devices are exempt from the 510(k) requirements. Premarket notifications are subject to user fees, unless a specific exemption applies.

Class III devices are deemed by the FDA to pose the greatest risk, such as those for which reasonable assurance of the device's safety and effectiveness cannot be assured solely by the general controls and special controls described above and that are life-sustaining or life-supporting. A PMA application must provide valid scientific evidence, typically extensive pre-clinical and clinical trial data and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications (and supplemental PMA applications) are subject to significantly higher user fees than are 510(k) premarket notifications.

Clinical Studies in Support of Development of a Medical Device

The types of clinical studies required for the development and approval of a medical device differ from those required for drug products. Clinical trials involving a drug product typically involve a sequential process of Phase 1, 2 and 3 clinical trials to test for the safety and efficacy of the product. The clinical development of a medical device, on the other hand, is often conducted in three different sequential phases, which may overlap or be combined. Those phases are a pilot study, which may also be referred to as an early feasibility study; a feasibility study; and a pivotal study.

- Pilot Study: A pilot study is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication. It may be used to evaluate the device design concept with respect to initial clinical safety and device functionality in a small number of subjects (generally fewer than ten initial subjects) when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from a pilot study may guide device modifications.

- Feasibility Study: A feasibility study is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. Because the study of a near-final or final device design takes place later in development than a pilot study, the FDA has indicated that it expects to see more nonclinical (or prior clinical) data in a feasibility study IDE application. A feasibility study does not necessarily need to be preceded by a pilot study.

- Pivotal Study: A pivotal study is a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. Evidence from one or more pivotal clinical studies generally serves as the primary basis for the determination of reasonable assurance of safety and effectiveness of the medical device of a PMA and FDA's overall benefit-risk determination. A pivotal study may or may not be preceded by a pilot study or feasibility study.

These three stages in the development of a medical device may be dependent on each other and conducting a thorough evaluation in one stage can make the next stage more straightforward. To determine which type of clinical study is appropriate to pursue, a manufacturer will consider several factors, such as the novelty of the device, the device's intended clinical use, the stability of the device design and the amount of test data available to support the IDE application. A pilot study is appropriate when device changes are expected and when, due to the novelty of the device or its intended use, a clinical study is expected to provide information that cannot be practically obtained through additional nonclinical assessments. A pilot study may also be appropriate even if a device or a prototype of the device has previously been used clinically for the intended clinical use. A feasibility study or a pivotal study may be more appropriate if the device design is near-final or final, respectively, depending on the amount of data available to justify the study.

510(k) Premarket Notification

To obtain 510(k) clearance, a manufacturer must submit a premarket notification demonstrating that the proposed device is "substantially equivalent" to a predicate device, which is a previously cleared 510(k) device or a pre-amendment device that was in commercial distribution before May 28, 1976, for which the FDA has not yet called for the submission of a PMA application. The FDA's 510(k) clearance pathway usually takes from three to 12 months from the date the application is submitted and filed with the FDA, but it can take significantly longer and clearance is never assured. The FDA has issued guidance documents meant to expedite review of a 510(k) and facilitate interactions between applicants and the agency. To demonstrate substantial equivalence, a manufacturer must show that the device has the same intended use as a predicate device and the same technological characteristics, or the same intended use and different technological characteristics and does not raise new questions of safety and effectiveness than the predicate device. Most 510(k)s do not require clinical data for clearance, but the FDA may request such data.

The FDA seeks to review and act on a 510(k) within 90 days of submission, but it may take longer if the agency finds that it requires more information to review the 510(k). If the FDA determines that the device is substantially equivalent to a predicate device, the subject device may be marketed. However, if the FDA concludes that a new device is not substantially equivalent to a predicate device, the new device will be classified in Class III and the manufacturer will be required to submit a PMA to market the product. Devices of a new type that the FDA has not previously classified based on risk are automatically classified into Class III by operation of section 513(f)(1) of the FDCA, regardless of the level of risk they pose. To avoid requiring PMA review of low- to moderate-risk devices classified in Class III by operation of law, Congress enacted section 513(f)(2) of the FDCA. This provision allows the FDA to classify a low- to moderate-risk device not previously classified into Class I or II, a process known as the *de novo* process. A company may apply directly to the FDA for classification of its device as *de novo* or may submit a de novo petition within 30 days of receiving a not substantially equivalent determination.

Modifications to a 510(k)-cleared medical device may require the submission of another 510(k). Modifications to a 510(k)-cleared device frequently require the submission of a traditional 510(k), but modifications meeting certain conditions may be candidates for FDA review under a special 510(k). If a device modification requires the submission of a 510(k), but the modification does not affect the intended use of the device or alter the fundamental technology of the device, then summary information that results from the design control process associated with the cleared device can serve as the basis for clearing the application. A special 510(k) allows a manufacturer to declare conformance to design controls without providing new data. When the modification involves a change in material, the nature of the "new" material will determine whether a traditional or special 510(k) is necessary.

Any modification to a 510(k)-cleared product that would constitute a major change in its intended use or any change that could significantly affect the safety or effectiveness of the device may, in some circumstances, requires the submission of a PMA, if the change raises complex or novel scientific issues or the product has a new intended use. A manufacturer may be required to submit extensive pre-clinical and clinical data depending on the nature of the changes.

The FDA requires every manufacturer to make the determination regarding the need for a new 510(k) submission in the first instance, but the FDA may review any manufacturer's decision. If the FDA disagrees with the manufacturer's determination and requires new 510(k) clearances or PMA approvals for modifications to previously cleared products for which the manufacturer concluded that new clearances or approvals are unnecessary, the manufacturer may be required to cease marketing or distribution of the products or to recall the modified product until it obtains clearance or approval, and the manufacturer may be subject to significant regulatory fines or penalties. In addition, the FDA is currently evaluating the 510(k) process and may make substantial changes to industry requirements.

Premarket Approval Application

The PMA process for approval to market a medical device is more complex, costly, and time consuming than the 510(k) clearance procedure. A PMA must be supported by extensive data, including technical information regarding device design and development, pre-clinical studies, clinical studies, manufacturing and controls information and labeling information, that demonstrates the safety and effectiveness of the device for its intended use. After a PMA is submitted, the FDA has 45 days to determine whether it is sufficiently complete to permit a substantive review. If the PMA is complete, the FDA will file the PMA. If the FDA accepts the application for filing, the agency will begin an in-depth substantive review of the application. By statute, the FDA has 180 days to review the application although, generally, review of the application often takes between one and three years, and may take significantly longer. If the FDA has questions, it will likely issue a first major deficiency letter within 150 days of filing. It may also refer the PMA to an FDA advisory panel for additional review, and will conduct a pre-approval inspection of the manufacturing facility to ensure compliance with the QSR, either of which could extend the 180-day response target. In addition, the FDA may request additional information or request the performance of additional clinical trials in which case the PMA approval may be delayed while the trials are conducted and the data acquired are submitted in an amendment to the PMA. Even with additional trials, the FDA may not approve the PMA application.

If the FDA's evaluations of both the PMA and the manufacturing facilities are favorable, the FDA will either issue an approval letter authorizing commercial marketing or an approvable letter that usually contains a number of conditions that must be met in order to secure final approval. If the FDA's evaluations are not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. The PMA process, including the gathering of clinical and nonclinical data and the submission to and review by the FDA, can take several years, and the process can be expensive and uncertain. Moreover, even if the FDA approves a PMA, the FDA may approve the device with an indication that is narrower or more limited than originally sought. The FDA can impose post-approval conditions that it believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. After approval of a PMA, a new PMA or PMA supplement may be required for a modification to the device, its labeling, or its

manufacturing process. PMA supplements often require submission of the same type of information as an initial PMA application, except that the supplement is limited to information needed to support any changes from the device covered by the approved PMA application and may or may not require as extensive technical or clinical data or the convening of an advisory panel. The time for review of a PMA supplement may vary depending on the type of change, but it can be lengthy. In addition, in some cases the FDA might require additional clinical data.

Investigational Device Exemption

A clinical trial is typically required for a PMA and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and nonsignificant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations.

Significant risk devices are, among other things, devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health and present a potential for serious risk to the health, safety or welfare of a subject. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Nonsignificant risk devices are devices that do not pose a significant risk to the human subjects. A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study.

An IDE application must be supported by appropriate data, such as animal and laboratory testing results, showing that it is safe to test the device in humans and that the testing protocol is scientifically sound. An IDE application is considered approved 30 days after it has been received by the FDA, unless the FDA otherwise informs the sponsor prior to 30 calendar days from the date of receipt that the IDE is approved, approved with conditions, or disapproved. The FDA typically grants IDE approval for a specified number of subjects to be enrolled at specified study centers. The clinical trial must be conducted in accordance with applicable regulations, including but not limited to the FDA's IDE regulations and GCP. The investigators must obtain subject informed consent, rigorously follow the investigational plan and study protocol, control the disposition of investigational devices, and comply with all reporting and record keeping requirements. A clinical trial may be suspended or terminated by the FDA, the IRB or the sponsor at any time for various reasons, including a belief that the risks to the study participants outweigh the benefits of participation in the trial. Approval of an IDE does not bind the FDA to accept the results of the trial as sufficient to prove the product's safety and efficacy, even if the trial meets its intended success criteria.

Humanitarian Use Device

When a medical device is intended to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year, a manufacturer may seek approval through a humanitarian device exemption, or HDE, application to market its product as a humanitarian use device, or HUD. This pathway provides an incentive for the development of devices for the treatment or diagnosis of diseases affecting small populations and where a manufacturer's research and development costs could exceed market return. Thus, the purpose of the HDE is to encourage device manufacturers to develop devices for rare conditions or diseases.

Prior to submitting the HDE application the device manufacturer must request HUD designation from the FDA's Office of Orphan Products Development. The FDA seeks to respond to the request within 45 days of submission. If granted, a manufacturer may file an HDE application for HUD approval.

An HDE application is similar to a PMA application but is exempt from the effectiveness requirements of a PMA. In submitting an HDE application a manufacturer is not required to include scientifically valid clinical investigation results demonstrating that the device is effective for its intended purpose. However, the

application must contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The manufacturer must also demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that the manufacturer could not otherwise bring the device to market. The FDA seeks to act on an HDE application within 75 days after accepting the HDE for filing.

If the FDA approves the HDE, the manufacturer may market the HUD. However, an HUD may only be used in facilities that have established an IRB to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. HUDs are also subject to specific labeling requirements identifying the device as a HUD device and noting that although the device is authorized by the FDA, the effectiveness of the device for the specific indication has not been demonstrated. Moreover, a manufacturer cannot charge an amount for an HDE approved device that exceeds the costs of research and development, fabrication, and distribution.

Expedited Access PMA

The FDA has proposed a program to provide earlier access to high-risk medical devices that are intended to treat or diagnose patients with serious conditions whose medical needs are unmet by current technology. The Expedited Access Premarket Approval Application for Unmet Medical Needs for Life Threatening or Irreversibly Debilitating Diseases or Conditions program, or EAP, allows for earlier and more interactive engagement with FDA staff. It also involves senior FDA management and a collaboratively developed plan for collecting scientific and clinical data to support approval—taken together, these features are meant to provide patients with earlier access to safe and effective medical devices by reducing the time associated with product development.

To be eligible for participation in the program, the medical device must be intended to treat or diagnose a life-threatening or irreversibly-debilitating disease or condition and represent one of the following:

- no approved alternative treatment exists;
- a breakthrough technology that provides a clinically meaningful advantage over existing technology;
- offers a significant, clinically meaningful advantage over existing approved alternatives; or
- availability of the device is in the patient's best interest.

The EAP must be accompanied by an acceptable data development plan that has been approved by the FDA. When utilizing the EAP program, the FDA will continue to apply the current approval standard of demonstrating a reasonable assurance of safety and efficacy.

Post-Marketing Restrictions and Enforcement

After a device is placed on the market, numerous regulatory requirements apply. These include, but are not limited to:

- submitting and updating establishment registration and device listings with the FDA;
- compliance with the QSR, which requires manufacturers to follow stringent design, testing, control, documentation, record maintenance, including maintenance of complaint and related investigation files, and other quality assurance controls during the manufacturing process;

- unannounced routine or for-cause device inspections by the FDA, which may include our suppliers' facilities; and

- labeling regulations, which prohibit the promotion of products for uncleared or unapproved or "off-label" uses and impose other restrictions on labeling; post-approval restrictions or conditions, including requirements to conduct post-market surveillance studies to establish continued safety data or tracking products through the chain of distribution to the patient level.

Under the FDA medical device reporting, or MDR, regulations, medical device manufacturers are required to report to the FDA information that a device has or may have caused or contributed to a death or serious injury or has malfunctioned in a way that would likely cause or contribute to death or serious injury if the malfunction of the device or a similar device of such manufacturer were to recur. The decision to file an MDR involves a judgment by the manufacturer. If the FDA disagrees with the manufacturer's determination, the FDA can take enforcement action.

Additionally, the FDA has the authority to require the recall of commercialized products in the event of material deficiencies or defects in design or manufacture. The authority to require a recall must be based on an FDA finding that there is reasonable probability that the device would cause serious adverse health consequences or death. Manufacturers may, under their own initiative, recall a product if any material deficiency in a device is found. The FDA requires that certain classifications of recalls be reported to the FDA within ten working days after the recall is initiated.

The failure to comply with applicable regulatory requirements can result in enforcement action by the FDA, which may include any of the following sanctions:

- untitled letters, warning letters, fines, injunctions or civil penalties;

- recalls, detentions or seizures of products;

- operating restrictions;

- delays in the introduction of products into the market;

- total or partial suspension of production;

- delay or refusal of the FDA or other regulators to grant 510(k) clearance or PMA approvals of new products;

- withdrawals of 510(k) clearance or PMA approvals; or

- in the most serious cases, criminal prosecution.

To ensure compliance with regulatory requirements, medical device manufacturers are subject to market surveillance and periodic, pre-scheduled and unannounced inspections by the FDA, and these inspections may include the manufacturing facilities of subcontractors.

Review and Approval of Combination Products in the United States

Certain products may be comprised of components that would normally be regulated under different types of regulatory authorities, and frequently by different Centers at the FDA. These products are known as combination products. Specifically, under regulations issued by the FDA, a combination product may be:

- a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products;

- a drug or device packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug or device where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

- any investigational drug or device packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Under the FDCA, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. That determination is based on the "primary mode of action" of the combination product. Thus, if the primary mode of action of a device-drug combination product is attributable to the drug product, the FDA Center responsible for premarket review of the drug product would have primary jurisdiction for the combination product. The FDA has also established an Office of Combination Products to address issues surrounding combination products and provide more certainty to the regulatory review process. That office serves as a focal point for combination product issues for agency reviewers and industry. It is also responsible for developing guidance and regulations to clarify the regulation of combination products, and for assignment of the FDA center that has primary jurisdiction for review of combination products where the jurisdiction is unclear or in dispute.

Review and Approval of Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of drug products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. Clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a drug under European Union regulatory systems, an applicant must submit a marketing authorization application, or MAA, either under a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated

as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various European Union member states where such product has not received marketing approval in any European Union member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Review and Approval of Medical Devices in the European Union

The European Union has adopted numerous directives and standards regulating, among other things, the design, manufacture, clinical trials, labeling, approval and adverse event reporting for medical devices. In the European Union, medical devices must comply with the Essential Requirements in Annex I to the EU Medical Devices Directive (Council Directive 93/42/EEC), or the Essential Requirements. Compliance with these requirements is a prerequisite to be able to affix the CE mark of conformity to medical devices, without which they cannot be marketed or sold in the European Economic Area, or EEA, comprised of the European Union member states plus Norway, Iceland, and Liechtenstein. Actual implementation of these directives, however, may vary on a country-by-country basis.

To demonstrate compliance with the Essential Requirements a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. Except for low risk medical devices, where the manufacturer can issue a CE Declaration of Conformity based on a self-assessment of the conformity of its products with the Essential Requirements, a conformity assessment procedure requires the intervention of a third-party organization designated by competent authorities of a European Union country to conduct conformity assessments, or a Notified Body. Notified Bodies are independent testing houses, laboratories, or product certifiers typically based within the European Union and authorized by the European member states to perform the required conformity assessment tasks, such as quality system audits and device compliance testing. The Notified Body would typically audit and examine the product's Technical File and the quality system for the manufacture, design and final inspection of the product before issuing a CE Certificate of Conformity demonstrating compliance with the relevant Essential Requirements.

Medical device manufacturers must carry out a clinical evaluation of their medical devices to demonstrate conformity with the relevant Essential Requirements. This clinical evaluation is part of the product's Technical File. A clinical evaluation includes an assessment of whether a medical device's performance is in accordance with its intended use, and that the known and foreseeable risks linked to the use of the device under normal conditions are minimized and acceptable when weighed against the benefits of its intended purpose. The clinical evaluation conducted by the manufacturer must also address any clinical claims, the adequacy of the device labeling and information (particularly claims, contraindications, precautions and warnings) and the suitability of related Instructions for Use. This assessment must be based on clinical data, which can be obtained from clinical studies conducted on the devices being assessed, scientific literature from similar devices whose equivalence with the assessed device can be demonstrated or both clinical studies and scientific literature.

With respect to implantable devices or devices classified as Class III in the European Union, the manufacturer must conduct clinical studies to obtain the required clinical data, unless relying on existing clinical data from similar devices can be justified. As part of the conformity assessment process, depending on the type of devices, the Notified Body will review the manufacturer's clinical evaluation process, assess the clinical evaluation data of a representative sample of the device's subcategory or generic group, or assess all the clinical evaluation data, verify the manufacturer's assessment of that data and assess the validity of the clinical evaluation report and the conclusions drawn by the manufacturer.

Even after a manufacturer receives a CE Certificate of Conformity enabling the CE mark on it products and the right to sell the products in the EEA countries, a Notified Body or a competent authority may require post-marketing studies of the products. Failure to comply with such requirements in a timely manner could result in the withdrawal of the CE Certificate of Conformity and the recall or withdrawal of the subject product from the European market.

A manufacturer must inform the Notified Body that carried out the conformity assessment of the medical devices of any planned substantial changes to the devices which could affect compliance with the Essential Requirements or the devices' intended purpose. The Notified Body will then assess the changes and verify whether they affect the product's conformity with the Essential Requirements or the conditions for the use of the devices. If the assessment is favorable, the Notified Body will issue a new CE Certificate of Conformity or an addendum to the existing CE Certificate of Conformity attesting compliance with the Essential Requirements. If it is not, the manufacturer may not be able to continue to market and sell the product in the EEA.

In the European Union, medical devices may be promoted only for the intended purpose for which the devices have been CE marked. Failure to comply with this requirement could lead to the imposition of penalties by the competent authorities of the European Union Member States. The penalties could include warnings, orders to discontinue the promotion of the medical device, seizure of the promotional materials and fines. Promotional materials must also comply with various laws and codes of conduct developed by medical device industry bodies in the European Union governing promotional claims, comparative advertising, advertising of medical devices reimbursed by the national health insurance systems and advertising to the general public.

Additionally, all manufacturers placing medical devices in the market in the European Union are legally bound to report any serious or potentially serious incidents involving devices they produce or sell to the competent authority in whose jurisdiction the incident occurred. In the European Union, manufacturers must comply with the EU Medical Device Vigilance System. Under this system, incidents must be reported to the relevant authorities of the European Union countries, and manufacturers are required to take Field Safety Corrective Actions, or FSCAs, to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. An incident is defined as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient or user or of other persons or to a serious deterioration in their state of health. An FSCA may include the recall,

modification, exchange, destruction or retrofitting of the device. FSCAs must be communicated by the manufacturer or its European Authorized Representative to its customers and to the end users of the device through Field Safety Notices. In September 2012, the European Commission adopted a proposal for a regulation which, if adopted, will change the way that most medical devices are regulated in the European Union, and may subject products to additional requirements.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the European Union provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with third-party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA will require applicable manufacturers of covered drugs, devices, drugs and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Employees

As of December 31, 2014, we had 48 full-time employees, of which 41 employees were engaged in research and development and seven employees provided general and administrative support. Of our employees, 27 have earned advanced degrees. Our employees are not represented by a labor union or covered by a collective bargaining agreement.

Our Corporate Information

We were incorporated under the laws of the State of Delaware on October 17, 2013 under the name Ikaria Development LLC. We changed our name to Bellerophon Therapeutics LLC on January 27, 2014. On

February 12, 2015, we converted from a Delaware limited liability company into a Delaware corporation and changed our name to Bellerophon Therapeutics, Inc. We currently have three wholly-owned subsidiaries: Bellerophon BCM LLC, a Delaware limited liability company; Bellerophon Pulse Technologies LLC, a Delaware limited liability company; and Bellerophon Services, Inc., a Delaware corporation. Our website address is www.bellerophon.com. The information contained on, or that can be accessed through, our website does not constitute part of this Annual Report on Form 10-K. We have included our website address in this Annual Report on Form 10-K solely as an inactive textual reference.

Our executive offices are located at 53 Frontage Road, Suite 301, Hampton, New Jersey 08827, and our telephone number is (908) 574-4770.

Available Information

We make available free of charge through our website our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. The information contained on, or that can be access through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 2 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net loss was approximately $46.2 million for the year ended December 31, 2012, $62.0 million for the year ended December 31, 2013 and $59.7 million for the year ended December 31, 2014. We do not know whether or when we will become profitable. We have not generated any revenues to date from product sales. We have not completed development of any product candidate and have devoted substantially all of our financial resources and efforts to research and development, including pre-clinical studies and clinical trials. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our deficit and working capital. We anticipate that our expenses will increase substantially if and as we:

- continue our research and clinical development of our INOpulse program for the treatment of PAH and PH-COPD and of our BCM program for the prevention of left ventricular remodeling following a STEMI;
- identify, develop and/or in-license additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- in the future, establish a manufacturing, sales, marketing and distribution infrastructure;
- maintain, expand and protect our intellectual property portfolio;
- add equipment and physical infrastructure to support our research and development;
- hire additional clinical, regulatory, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and any future commercialization efforts and personnel and infrastructure necessary to help us comply with our obligations as a public company.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. We do not expect to generate significant revenue unless and until we are able to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. This will require us to be successful in a range of challenging activities, including completing pre-clinical studies and clinical trials of our product candidates, discovering additional product candidates,

obtaining regulatory approval for our product candidates, manufacturing, marketing and selling any products for which we may obtain regulatory approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. We are in the early stages of most of these activities and have not yet commenced other of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA or the EMA to perform trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could cause our stockholders to lose all or part of their investment in us.

In addition, our recurring losses from operations, accumulated deficit and our need to raise additional financing in order to continue to fund our operations, raise substantial doubt about our ability to continue as a going concern. Given our planned expenditures for the next several years, including, without limitation, expenditures in connection with our clinical trials, our independent registered public accounting firm may conclude that there is substantial doubt regarding our ability to continue as a going concern.

Our very limited operating history as a stand-alone company may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability.

We were formed as a wholly-owned subsidiary of Ikaria in October 2013 and became a stand-alone company in February 2014 following the Spin-Out and, as such, have a very limited operating history as a stand-alone company. Prior to the Spin-Out, Ikaria assisted us by providing financing and certain corporate functions. Following the Spin-Out, Ikaria has no obligation to provide assistance to us other than on an interim basis as provided for in the agreements we entered into in connection with the Spin-Out. See “Certain Relationships and Related Person Transactions—Relationship with Ikaria.”

Our operations to date have been limited to organizing and staffing our company, developing and securing our technology, and undertaking pre-clinical studies and clinical trials of our product candidates. We have not yet demonstrated the ability to successfully operate as a stand-alone company or to complete development of any product candidates, obtain marketing approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions our stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing products.

Assuming we obtain marketing approval for any of our product candidates, we will need to transition from a company with a research and development focus to a company capable of supporting commercial activities or we will need to enter into strategic partnerships. We may encounter unforeseen expenses, difficulties, complications and delays and may not be successful in such a transition.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we initiate additional clinical trials of our INOpulse and BCM product candidates and continue research and development and seek regulatory approval for these and potentially other product candidates. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. In particular, the costs that may be required for the manufacture of any product candidate that receives marketing approval may be substantial. In addition, relative to previous years when we operated as a private company, we expect to incur additional costs in 2015 and future years associated with operating as a public company. As of December 31, 2014, we had cash and cash equivalents and restricted cash of $27.6 million. From the inception of our business through December 31, 2014, Ikaria made cumulative investments of $177.5 million in us and contributed an additional $80.0 million in cash to us in connection with the Spin-Out. Now that we are a stand-alone company, any additional funding will need to come from another source. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We plan to use our current cash and cash equivalents and restricted cash, including the net proceeds of our initial public offering, primarily to fund our ongoing research and development efforts. We will be required to expend significant funds in order to advance development of our INOpulse and BCM product candidates and any other potential product candidates. Our existing cash and cash equivalents and restricted cash, including the net proceeds of our initial public offering, will not be sufficient to fund all of the efforts that we plan to undertake, such as the further development of INOpulse for PH-COPD or BCM, or to fund completion of clinical development or commercialization of any of our product candidates. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations or licensing arrangements or other sources. Adequate additional funding may not be available to us on acceptable terms or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our existing cash and cash equivalents and restricted cash as of December 31, 2014, together with the net proceeds of our initial public offering, will enable us to fund our planned operating expenses and capital expenditure requirements at least into mid-2016. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our future capital requirements will depend on many factors, including:

- the progress and results of our current and planned clinical trials of our INOpulse and BCM product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of operating as a stand-alone company;
- the cost and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of any product candidates for which we receive marketing approval;
- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the scope, progress, results and costs of discovery, pre-clinical development and clinical trials for any other product candidates;
- the extent to which we acquire or in-license other product candidates and technologies;
- our headcount growth and associated costs; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting pre-clinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings and/or license and development agreements with collaboration partners. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our stockholders may be materially diluted, and the terms of such securities could include liquidation or other preferences that adversely affect the rights of our stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specified actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. If we raise funds through collaborations, strategic partnerships or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us.

Risks Related to Our Business and Industry

We may be unable to make, on a timely or cost-effective basis, the changes necessary to operate as a stand-alone company, and we may experience increased or unexpected costs after the Spin-Out or as a result of the Spin-Out.

We have historically operated as part of Ikaria's broader corporate organization, and Ikaria has assisted us by providing certain corporate functions. However, following the Spin-Out, Ikaria is contractually obligated to provide to us only those services specified in a transition services agreement, or the TSA, a services agreement, or the 2015 Services Agreement, and the other agreements we entered into with Ikaria to govern our relationship following the Spin-Out. See "Certain Relationships and Related Person Transactions—Relationship with Ikaria" for a summary of these agreements. The TSA and the 2015 Services Agreement provide for certain

services to be provided until February 2016. We may be unable to replace in a timely manner or on comparable terms the services or other benefits that Ikaria previously provided to us that are not specified in the TSA, the 2015 Services Agreement or the other agreements. Also, upon the termination of the services provided under the TSA or other agreements, such services will be provided internally or by unaffiliated third parties, and we expect that in some instances, we will incur higher costs to obtain such services than we incurred under the terms of such agreements. Ultimately, we may be unable to replace in a timely manner or on comparable terms the services specified in such agreements. In addition, during the transitional services period, we will rely, in part, on the same executive team at Ikaria that also will continue to manage the business of Ikaria during such time, and there may be conflicting demands on their time, which could result in an inadequate level of attention to the demands of our business. If Ikaria and its employees do not continue to perform effectively the transition services and the other services that are called for under the TSA, the 2015 Services Agreement and other agreements, we may not be able to operate our business effectively and our business and financial condition could be adversely affected.

On March 5, 2015, Mallinckrodt and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the TSA imposes binding obligations on Ikaria to perform in accordance with the TSA's terms, it is possible that following completion of the sale, as the new owner's influence on Ikaria's operations increases, Ikaria may not continue to provide the same level of performance under the TSA as Ikaria has provided to date. Moreover, to the extent that we desire to extend, renew or expand the scope of the TSA, it is also possible that Ikaria will not be willing to do so on reasonable terms, or at all. In any of these circumstances, our business, product development and financial statements could be materially adversely affected.

Prior to the Spin-Out, we utilized the executive management team and administrative resources of Ikaria. Many daily functions were performed by Ikaria, including those related to the preparation of our financial statements and the engagement of auditors to audit our financial statements, which have become our responsibility following the Spin-Out. We may need to acquire assets and resources in addition to those provided to us by Ikaria, and we may face difficulty in integrating newly acquired assets into our business. Additionally, as a stand-alone company, we no longer have access to Ikaria's financial resources. Instead, our ability to fund our capital needs will depend on our ongoing ability to generate cash from operations, enter into partnering arrangements, obtain debt financing and access capital markets, which are subject to general economic, financial, competitive, regulatory and other factors that are beyond our control. Our business, financial condition and results of operations could be harmed, possibly materially, if we have difficulty operating as a stand-alone company, fail to acquire necessary capital or assets that prove to be important to our operations, or are unable to enter into partnering or other business development arrangements.

We are also currently incurring and expect to continue to incur additional incremental expenses associated with being a stand-alone company. These incremental pretax expenses were approximately $5.0 million for the year ended December 31, 2014.

Our historical financial information is not necessarily representative of the results we would have achieved as a stand-alone company and may not be a reliable indicator of our future results.

The historical financial information we have included in this report may not reflect what our results of operations, financial position and cash flows would have been had we been a stand-alone company during the periods presented. This is primarily because:

- our historical financial information reflects allocations for services historically provided to us by Ikaria, which allocations may not reflect the costs we will incur for similar services in the future as a stand-alone company; and

- our historical financial information does not reflect changes that we expect to incur in the future as a result of our separation from Ikaria and from reduced economies of scale, including changes in the cost structure, personnel needs, financing and operations of our business.

In addition, as a newly public company, we are also responsible for the additional costs associated with being a public company, including costs related to corporate governance and having listed and registered securities. Therefore, our historical financial information may not be indicative of our future performance as a stand-alone public company.

For additional information about our past financial performance and the basis of presentation of our financial statements, please see "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K.

The ownership by certain of our executive officers and directors of equity of Ikaria, as well as the continued roles of certain of our directors with Ikaria, may create, or may create the appearance of, conflicts of interest.

Because of their current or former positions with Ikaria, our chief business officer, Manesh Naidu, our chief clinical development officer, Reinilde Heyrman, our chief scientific officer, Martin Meglasson, our treasurer, David Abrams, and one of our directors, Daniel Tassé, own equity in Ikaria. In addition, two of our directors, Matthew Holt and Adam B. Weinstein, may be deemed to beneficially own equity in Ikaria. Such equity ownership may create, or may create the appearance of, conflicts of interest. The individual holdings of equity of Ikaria may be significant for some of these persons compared to such person's total assets. Ownership by certain of our executive officers and directors of equity of Ikaria creates, or may create the appearance of, conflicts of interest when these officers or directors are faced with decisions that could have different implications for Ikaria than the decisions have for us. In addition, Matthew Holt and Daniel Tassé are currently serving on our board of directors as well as Ikaria's board of directors, and Mr. Tassé is currently serving as the chief executive officer of Ikaria. The continued service at both companies creates, or may create the appearance of, conflicts of interest when these directors are faced with decisions that could have different implications for Ikaria than the decisions have for us, such as the allocation of time and resources to the provision of transitional services to us by Ikaria pursuant to the TSA, the 2015 Services Agreement and the other agreements.

We face substantial competition from other pharmaceutical, biotechnology and medical device companies and our operating results may suffer if we fail to compete effectively.

The pharmaceutical, biotechnology and medical device industries are highly competitive. There are many pharmaceutical, biotechnology and medical device companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our product candidates. In addition, other companies are increasingly looking at the cardiopulmonary and cardiac disease market as a potential opportunity. Currently, there are 12 drugs approved for the treatment of PAH, within the following categories: prostacyclin and prostacyclin analogs (including Flolan® (epoprostenol), which is marketed by GlaxoSmithKline, Tyvaso® (treprostinil), Orenitram® (treprostinil) and Remodulin® (treprostinil), which are marketed by United Therapeutics Corporation, and Ventavis® (iloprost) and Veletri® (epoprostenol), which are marketed by Actelion Pharmaceuticals US, Inc., or Actelion), phosphodiesterase type-5 inhibitors (including Adcirca® (tadalafil), which is marketed by United Therapeutics Corporation, and Revatio® (sildenafil), which is marketed by Pfizer Inc.), endothelin receptor antagonists (including Letairis® (ambrisentan), which is marketed by Gilead Sciences, Inc., and Opsumit® (macitentan) and Tracleer® (bosentan), which are marketed by Actelion) and a soluble guanylate cyclase stimulator (Adempas® (riociguat), which is marketed by Bayer HealthCare Pharmaceuticals Inc.). Actelion recently submitted an NDA to the FDA for selexipag, a selective prostacyclin receptor agonist. There are also other treatments in Phase 1 and Phase 2 clinical development, including other nitric oxide generation and delivery systems, including GeNOsyl, which is being developed by GeNO LLC, and a nebulized formulation of nitrite, which is being developed by Mast Therapeutics.

Currently, there are no approved therapies for treating PH-COPD, and the only generally accepted treatments are LTOT, pulmonary rehabilitation and lung transplant, and we are not aware of any therapies for PH-COPD in advanced clinical development.

There are no generally accepted products approved for structural support to prevent cardiac remodeling following an AMI. Other product candidates that are currently in clinical development include stem cell therapies to restore heart muscle cells following an AMI, with large Phase 3 trials expected to be completed in 2018 or 2019. We do not expect BCM to compete with, or replace, current treatments for congestive heart failure following AMI, but instead believe it will become part of the treatment regimen used in conjunction with other therapies. In addition, because BCM can be delivered by a minimally invasive percutaneous coronary intervention procedure, we do not believe it will directly compete with devices that are used to treat congestive heart failure, which are designed for administration during open heart surgery or by intra-cardiac injection involving a thoracotomy procedure. These include: mesh restraining devices, for example HeartNet; injectable biopolymers, for example Algisyl-LVR; and implantable electro stimulation devices, for example, CardioFit. In addition, volume reduction surgery or cardiac assist devices, or pumps, are sometimes used to treat patients with congestive heart failure.

Many of our competitors, either alone or through their strategic partners, have substantially greater name recognition and financial, technical, manufacturing, marketing and human resources than we do and significantly greater experience and infrastructure in the research and clinical development of medical products, obtaining FDA and other regulatory approvals of those products, and commercializing those products around the world. Additional mergers and acquisitions in the pharmaceutical, biotechnology and medical device industries may result in even more resources being concentrated in our competitors. Large pharmaceutical and medical device companies in particular have extensive expertise in pre-clinical and clinical testing and in obtaining regulatory approvals for medical products. In addition, academic institutions, government agencies, and other public and private organizations conducting research may seek patent protection with respect to potentially competitive products or technologies. These organizations may also establish exclusive collaborative or licensing relationships with our competitors. Accordingly, our competitors may be more successful than we may be in obtaining approval for inhaled nitric oxide products and achieving widespread market acceptance. We anticipate that we will face intense and increasing competition as new products and technologies become available.

We will not be able to compete effectively unless we successfully:

- design, develop and commercialize products that are superior to other products in the market;
- attract qualified scientific, medical, sales and marketing, engineering and commercial personnel;
- obtain patent and/or other proprietary protection for our processes and product candidates; and
- obtain required regulatory approvals.

It is also possible that Ikaria will seek to develop and commercialize inhaled nitric oxide products or product candidates in PAH, PH-COPD and/or PH-IPF. While a subsidiary of Ikaria has granted to us an exclusive license to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF and the scope of that license includes certain technology developed or acquired by that subsidiary after the date of the license agreement, the license does not include technology developed or acquired by other subsidiaries or affiliates of Ikaria. Because Ikaria and its subsidiaries and affiliates are not subject to any non-competition obligations in our favor, it is possible that these other subsidiaries or affiliates of Ikaria may seek to develop or commercialize inhaled nitric oxide or other products or product candidates, using technology not exclusively licensed to us, that are competitive with our products or product candidates.

Risks Related to the Discovery, Development and Commercialization of Our Product Candidates

We are dependent on the success of our INOpulse and BCM product candidates and our ability to develop, obtain marketing approval for and successfully commercialize these product candidates. If we are unable to develop, obtain marketing approval for or successfully commercialize our product candidates, either alone or through a collaboration, or experience significant delays in doing so, our business could be materially harmed.

We currently have no products approved for sale and have invested a significant portion of our efforts and financial resources in the development of our INOpulse for PAH, INOpulse for PH-COPD and BCM product candidates. Our prospects are substantially dependent on our ability to develop, obtain marketing approval for and successfully commercialize these product candidates. The success of our product candidates will depend on, among other things, our ability to successfully complete clinical trials of each product candidate. The clinical trial process is uncertain, and failure of one or more clinical trials can occur at any stage of testing. For example, although we believe our recently completed Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD support advancement into a Phase 3 and a Phase 2b clinical trial, respectively, the primary endpoints for both INOpulse for PAH and INOpulse for PH-COPD were not statistically significant for any of the doses tested.

In addition to the successful completion of clinical trials, the success of our product candidates will also depend on several other factors, including the following:

- receipt of marketing approvals from the FDA or other applicable regulatory authorities;
- establishment of supply arrangements with third-party raw materials suppliers and manufacturers;
- establishment of arrangements with third-party manufacturers to obtain finished drug products that are appropriately packaged for sale;
- the performance of our future collaborators for one or more of our product candidates, if any;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally;
- protection of our rights in our intellectual property portfolio;
- launch of commercial sales if and when our product candidates are approved;
- a continued acceptable safety profile of our product candidates following any marketing approval;
- commercial acceptance, if and when approved, by patients, the medical community and third-party payors;
- establishing and maintaining pricing sufficient to realize a meaningful return on our investment; and
- competition with other products.

If we are unable to develop, receive marketing approval for, or successfully commercialize our product candidates, or experience delays as a result of any of these factors or otherwise, our business could be materially harmed.

Clinical trials involve a lengthy and expensive process with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We recently completed Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD and are currently conducting a clinical trial of BCM. The risk of failure of all of our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of severe or medically or commercially unacceptable adverse events, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable non-U.S. regulatory authority that a drug product is not approvable. For example, although we believe our recently completed Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD support advancement into a Phase 3 and a Phase 2b clinical trial, respectively, the primary endpoints for both INOpulse for PAH and INOpulse for PH-COPD were not statistically significant for any of the doses tested.

It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case. Also, the exclusion criteria we define may not sufficiently rule out patients who are at a higher risk of being harmed by the treatment. For example, our exclusion criteria for pre-existing left heart dysfunction in our recently completed Phase 2 INOpulse clinical trials may not rule out patients who may experience an adverse event related to left ventricular function due to exposure to nitric oxide. In addition, patients who are not excluded for reactive pulmonary vasculature when exposed to nitric oxide may still experience pulmonary hypertension.

The outcome of pre-clinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results, particularly when earlier trials are small, open-label or non-placebo-controlled trials and in trials that have different endpoints than earlier trials. For example, we are relying on the results from a 32-patient Phase 2 PH-COPD trial, conducted in Austria, as part of our clinical development program of INOpulse for PH-COPD, and we may not be able to replicate the results of this trial in a larger trial or in a trial that uses a clinical endpoint rather than the anatomical endpoints used in the 32-patient trial. Similarly, for BCM, we are using the results of the 27-patient pilot trial conducted by BioLineRx Ltd. that used anatomical changes to measure efficacy and did not have a control group as support for our larger ongoing clinical trial, which may not achieve the same results as the BioLineRx Ltd. trial. Many companies in the biotechnology, pharmaceutical and medical device industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we cannot be certain that we will not face such setbacks.

The design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced or completed. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, pre-clinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we believe that the results of clinical trials for our product candidates warrant

marketing approval, the FDA or comparable non-U.S. regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the clinical trial protocols and the rate of dropout among clinical trial participants. Any Phase 3 or other clinical trials that we may conduct may not demonstrate the efficacy and safety necessary to obtain regulatory approval to market our product candidates.

INOpulse is a sophisticated electro-mechanical device comprised of components that may fail or deteriorate over time or with improper use. If we experience problems with, failure of, or delays in obtaining any INOpulse components, our business could be materially adversely harmed.

Because INOpulse is a sophisticated electro-mechanical device, the parts which comprise the device are subject to sudden failure or to wear and tear, which may result in decreased function or failure of those parts over time. Although we perform scheduled, preventive maintenance on our drug delivery system to limit device failures, and additional maintenance as needed whenever a user reports a device malfunction, components of our devices may fail. In addition, although we have designed INOpulse to be simple and easy to use and will provide user manuals and other training materials, users of INOpulse may use the devices improperly, which could cause the devices to fail or otherwise not work properly.

There are several components in INOpulse that are custom designed or assembled for us. We are dependent on a single company to supply us with some of these components. While we believe there are alternative suppliers from which we could purchase most of these components, there is a risk that a single-source supplier could fail to deliver adequate supply, or could suffer a business interruption that could affect our supply of these components.

We obtain some of the components for INOpulse through individual purchase orders executed on an as needed basis rather than pursuant to long-term supply agreements. Our business, financial condition or results of operations could be adversely affected if any of our principal third-party suppliers or manufacturers experience production problems, lack of capacity or transportation disruptions or otherwise cease producing such components.

We are transitioning our INOpulse delivery system to a next generation device that was not utilized in our recently completed INOpulse Phase 2 clinical trials. Failure by the FDA or other regulatory authority to support the transition and bridging strategy for our transition to the new device could increase our development costs and/or delay commencement of our future clinical trials of INOpulse.

Our recently completed INOpulse Phase 2 clinical trials utilized the first generation INOpulse DS device. We are near completion of a second generation INOpulse device, the Mark2, and we plan to transition our INOpulse delivery system from INOpulse DS to the Mark2 for any future INOpulse clinical trials. To facilitate the transition from our existing INOpulse DS device to the Mark2 in our clinical program, we plan to conduct comparability testing of nitric oxide dosing with the Mark2 as compared to the INOpulse DS device. This testing will include a comparison of critical parameters, including pulse width and nitric oxide output. We will also assess whether the Mark2 will meet the performance specifications of the INOpulse DS device in addition to Mark2-specific requirements. In addition, we are developing a bridging test report that we expect to include in the regulatory package that we anticipate submitting to the FDA during the first half of 2015 to gain approval for the device transition. We discussed our strategy with the FDA during a meeting in May 2013, and we believe that, assuming the Mark2 meets the specified comparability parameters, this testing will be sufficient to gain FDA approval to use the Mark2 in future clinical trials, as planned. The FDA may not agree that our data support transition to this new device, in which case we may be required to provide additional data, perform a revised bridging assessment or repeat the Phase 2 clinical trial, any of which could increase our development

costs and/or delay or prevent commencement of these future clinical trials. In addition, even if the FDA accepts our transition plan, use of the Mark2 in future clinical trials could produce results that are different than those we would expect based on the results from the Phase 2 clinical trial using the INOpulse DS device.

We intend to conduct, and may in the future conduct, clinical trials for certain of our product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

We have conducted, and may in the future choose to conduct, one or more of our clinical trials outside the United States. For example, our Phase 2 clinical trial of INOpulse for PAH included sites in Canada and our clinical trial of BCM includes sites in Europe, Canada, Australia and Israel.

Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with GCP in the case of drug trials, or the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the human subjects, in the case of device trials. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. Generally, the patient population for any clinical trials conducted outside of the United States must be representative of the population for whom we intend to seek approval in the United States. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from trials conducted outside of the United States. If the FDA does not accept the data from our Phase 2 clinical trial of INOpulse for PAH in Canada or our clinical trial of BCM in Europe, Canada, Australia or Israel, or any future trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay or permanently halt our development of INOpulse for PAH and BCM or any future product candidates.

In addition, the conduct of clinical trials outside the United States could have a significant impact on us. Risks inherent in conducting international clinical trials include:

- foreign regulatory requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple foreign regulatory schema;
- foreign exchange fluctuations; and
- diminished protection of intellectual property in some countries.

If clinical trials of our product candidates fail to demonstrate safety and efficacy of our product candidates to the satisfaction of the FDA and comparable non-U.S. regulators, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of these product candidates.

We are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Comparable non-U.S. regulatory authorities, such as the EMA, impose similar restrictions. We may never receive such approvals. We must complete extensive pre-clinical studies and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We have not previously submitted an NDA to the FDA or similar drug approval filings to comparable non-U.S. regulatory authorities for any of our product candidates.

Any inability to successfully complete pre-clinical and clinical development could result in additional costs to us and impair our ability to generate revenues from product sales. In addition, if (1) we are required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we contemplate, (2) we are unable to successfully complete clinical trials of our product candidates or other testing, (3) the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, such as in our Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD, or (4) there are unacceptable safety concerns associated with our product candidates, we, in addition to incurring additional costs, may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as we intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- be required to remove the product from the market after obtaining marketing approval.

For example, the FDA has granted us an IDE for our ongoing clinical trial of BCM, which we refer to as our PRESERVATION I trial, which currently limits at 60 the number of patients we can enroll in the United States. This limitation is due to the novelty of BCM and the lack of prior data on administration to human patients of four milliliters of BCM that we are using in the trial because we did not conduct a pilot study of BCM with the four milliliter volume. Due to the lack of a pilot study or other data supporting the safety or efficacy of four milliliters of BCM in human patients, the FDA may require that, prior to approval, we conduct additional trials of BCM or that we provide additional data to support the safety and/or efficacy of four milliliters of BCM in human patients.

In addition, the FDA has asked us to conduct a study to test the environmental impact of using INOpulse at home. When inhaled nitric oxide is administered through INOpulse, a small portion of the nitric oxide will be exhaled or otherwise emitted and could react with oxygen in room air to form nitrogen dioxide, which is an environmental pollutant. The study will measure the nitrogen dioxide in the room air with use of INOpulse under actual or simulated patient use conditions. If the FDA or other regulatory authority requires us to conduct additional testing or determines that an unacceptable amount of nitrogen dioxide is formed through the use of INOpulse, we may be required to alter the design of INOpulse, which may not be possible, and the clinical development timeline for INOpulse may be delayed or prove to be more costly than we currently anticipate.

If we experience any of a number of possible unforeseen events in connection with clinical trials of our product candidates, potential marketing approval or commercialization of our product candidates could be delayed or prevented.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent marketing approval of our product candidates, including:

- clinical trials of our product candidates may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, patient enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;

- our third-party contractors, including those manufacturing our product candidates or components or ingredients thereof or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner or at all;

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

- we may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;

- patients who enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to withdraw such patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;

- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of a product candidate;

- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their respective standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar drug or drug candidate;

- the FDA or comparable non-U.S. regulatory authorities may disagree with our clinical trial design or our interpretation of data from pre-clinical studies and clinical trials;

- the FDA or comparable non-U.S. regulatory authorities may find regulatory non-compliance with the manufacturing processes or facilities of third-party manufacturers with which we enter into agreements for clinical and commercial supplies;

- the supply or quality of raw materials or manufactured product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and

- the approval policies or regulations of the FDA or comparable non-U.S. regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

Product development costs for us will increase if we experience delays in testing or pursuing marketing approvals and we may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any pre-clinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. For example, although we recently completed a Phase 2 clinical trial for INOpulse for PH-COPD, we are currently evaluating our options for further Phase 2 development in this indication. Significant pre-clinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to

successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

If we experience delays or difficulties in the enrollment of patients in clinical trials, we may not achieve our clinical development on our anticipated timeline, or at all, and our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for our INOpulse or BCM product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the proximity of patients to clinical sites;
- the eligibility criteria for the trial;
- the design of the clinical trial;
- limitations placed on enrollment by regulatory authorities;
- efforts to facilitate timely enrollment;
- competing clinical trials; and
- clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new product candidates that may be approved for the indications we are investigating.

For example, we may experience difficulty enrolling our clinical trials, including, but not limited to, any future clinical trials of INOpulse for PAH, which is an orphan disease due to the small number of patients who suffer from PAH, or any future clinical trials of INOpulse for PH-COPD because such trials may require that patients meet the restrictive enrollment criteria, such as having been diagnosed with both COPD and pulmonary hypertension, be undergoing treatment with LTOT and not having significant left ventricular dysfunction.

In addition, with respect to our PRESERVATION I trial, the FDA has limited us to enrolling a maximum of 60 patients in the United States. This limitation is due to the novelty of BCM and the lack of prior data on the administration to human patients of four milliliters of BCM that we are using in the trial because we did not conduct a pilot study of BCM with this dose. We will need to obtain the FDA's approval of any expansion of this U.S. enrollment cap, and such approval would likely be based on our submission of data to the FDA supporting the safety of four milliliters of BCM in human patients, if any. The Israeli Ministry of Health is also requiring that we submit to it additional safety data once 70 patients are enrolled in Israel.

Our inability to enroll a sufficient number of patients for our clinical trials could result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, delay or halt the development of and approval processes for our product candidates and jeopardize our ability to achieve our clinical development timeline and goals, including the dates by which we will commence, complete and receive results from clinical trials. Enrollment delays may also delay or jeopardize our ability to commence sales and generate revenues from our product candidates. Any of the foregoing could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

We may not obtain orphan drug exclusivity, or we may not receive the full benefit of orphan drug exclusivity even if we obtain such exclusivity.

Regulatory authorities in some jurisdictions, including the United States and European Union, may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States who have been diagnosed as having the disease or condition at the time of the submission of the request for orphan drug designation. The FDA has granted orphan drug designation to our nitric oxide program for the treatment of PAH. Accordingly, the first company to receive FDA approval for nitric oxide for the treatment of PAH will obtain seven years of marketing exclusivity, during which time the FDA may not approve another product containing nitric oxide as its active ingredient for the treatment of PAH, unless such product is shown to be clinically superior.

Even though we have obtained orphan drug designation for our nitric oxide program to treat PAH, and even if we obtain orphan drug designation for our product candidates in other indications or for our future product candidates, due to the uncertainties associated with developing pharmaceutical products, we may not be the first to obtain marketing approval for any particular orphan indication, or we may not obtain approval for an indication for which we have obtained orphan drug designation. Further, even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not protect the product effectively from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process. Orphan drug exclusivity may be lost if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Serious adverse events or undesirable side effects or other unexpected properties of our product candidates may be identified during development that could delay or prevent the product candidate's marketing approval.

Serious adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable non-U.S. regulatory authorities. If any of our product candidates is associated with serious adverse events or undesirable side effects or has properties that are unexpected, we may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many drugs or devices that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the drug or device.

For example, in our recently completed Phase 2 clinical trial for INOpulse for PAH, serious adverse events were reported for four patients in the 25 mcg/kg ideal body weight/hour, or mcg, low-dose active treatment arm, including bacteremia, myelodysplastic syndrome, increased shortness of breath and dyspnea, one of which was assessed as possibly related to trial therapy. In the 75 mcg high-dose active treatment arm, nine patients had serious adverse events. The most common serious adverse events reported were syncope and bronchitis/tracheobronchitis, one of which was assessed as possibly related to trial therapy. Discontinuation of trial therapy due to adverse events occurred for two patients in the 75 mcg arm and one subject in the 25 mcg arm. Additional or more serious adverse events, undesirable side effects or other unexpected properties of INOpulse for PAH or our other product candidates could arise or become known either during further clinical development. If such an event occurs during development, clinical trials for our product candidates could be

suspended or terminated and the FDA or comparable foreign regulatory authorities could order us or our collaborators to cease further development, require us to conduct additional clinical trials or other tests or studies or deny approval of the applicable product candidate. Further, pending discussions with regulatory authorities, we may be required to conduct a drug-drug interaction study of INOpulse for PH-COPD. We expect the FDA to require us primarily to study interactions with long-acting beta agonists, which is the only class of COPD drug that has been identified as having potential adverse cardiac side effects, to confirm that pulsed inhaled nitric oxide does not increase systemic bio-availability of inhaled beta agonists. If the results of such a study indicate increased bioavailability that we are not able to address to the satisfaction of the FDA, marketing approval of INOpulse for PH-COPD, if any, may be limited to patients who do not use long-acting beta agonists.

Additionally, INOpulse is an extension of the technology that is used in hospitals to deliver inhaled nitric oxide to neonates with a form of pulmonary hypertension called persistent pulmonary hypertension of the newborn. Persistent pulmonary hypertension is an FDA-approved use of inhaled nitric oxide, which is currently marketed by Ikaria as INOmax. Because INOpulse draws on the established efficacy and safety of INOmax, if any serious adverse events or undesirable side effects or other unexpected properties of INOmax or other inhaled nitric oxide delivery systems developed by Ikaria are identified, INOpulse may be adversely affected and we may be required to interrupt, delay or halt our INOpulse clinical trials.

We may not be successful in our efforts to identify or discover additional potential product candidates.

A significant portion of the research that we are conducting involves the development of innovative approaches to the pulsed delivery of nitric oxide. Our drug-device discovery efforts may not be successful in creating drugs or devices that have commercial value or therapeutic utility. Our research programs may initially show promise in creating potential product candidates, yet fail to yield viable product candidates for clinical development for a number of reasons, including that potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be product candidates that will receive marketing approval and achieve market acceptance. Currently, we are dependent on Ikaria for our business development functions pursuant to the TSA and lack the capability to bring such functions in-house. Accordingly, if Ikaria does not perform such business development functions effectively, our business and prospects may be materially and adversely affected.

Our research programs to identify new product candidates will require substantial technical, financial and human resources. We may be unsuccessful in our efforts to identify new potential product candidates. In addition, we may focus our efforts and resources on one or more potential product candidates that ultimately prove to be unsuccessful.

Pursuant to the terms of our license agreement with Ikaria, we only have the right to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and PH-IPF; Ikaria retains the right to develop and commercialize inhaled nitric oxide products, including pulsed products, in all other indications. Additionally, we are limited in the scope of potential product candidates that we can identify or discover due to non-competition agreements that we entered into with Ikaria. Pursuant to these agreements, we and each of our subsidiaries agreed not to engage, anywhere in the world, in any manner, directly or indirectly, until the earlier of five years after the effective date of such non-competition agreement or the date on which Ikaria and all of its subsidiaries are no longer engaged in such business, in:

- the development, manufacture, commercialization, promotion, sale, import, export, servicing, repair, training, storage, distribution, transportation, licensing, or other handling or disposition of any product or service (including, without limitation, any product or service that utilizes, contains or includes nitric oxide for inhalation, a device intended to deliver nitric oxide or a service that delivers or supports the delivery of nitric oxide), bundled or unbundled, for or used in connection with (a) the diagnosis, prevention or treatment, in both adult and/or pediatric populations, and whether in- or out-patient, of: (i) hypoxic respiratory failure associated with pulmonary hypertension,

(ii) pulmonary hypertensive episodes and right heart failure associated with cardiovascular surgery, (iii) bronchopulmonary dysplasia, (iv) the management of ventilation-perfusion mismatch in acute lung injury, (v) the management of ventilation-perfusion mismatch in acute respiratory distress syndrome, (vi) the management of pulmonary hypertension episodes and right heart failure in congestive heart failure, (vii) pulmonary edema from high altitude sickness, (viii) the management of pulmonary hypertension episodes and right heart failure in pulmonary or cardiac surgery, (ix) the management of pulmonary hypertension episodes and right heart failure in organ transplant, (x) sickle cell vaso-occlusive crisis, (xi) hypoxia associated with pneumonia or (xii) ischemia-reperfusion injury or (b) the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital; or

- any and all development, manufacture, commercialization, promotion, sale, import, export, storage, distribution, transportation, licensing, or other handling or disposition of any terlipressin or any other product within the pressin family, (a) intended to treat (i) hepatorenal syndrome in any form, (ii) bleeding esophageal varices or (iii) septic shock or (b) for or in connection with the management of low blood pressure.

In the event that we or one of our subsidiaries materially breach the provisions of the non-competition agreements and do not cure such breach within 30 days after receiving written notice thereof from Ikaria, Ikaria will have the right to terminate the license agreement.

If we are unable to identify suitable additional compounds for pre-clinical and clinical development, or at all, our ability to develop product candidates and obtain product revenues in future periods could be compromised, which could result in significant harm to our financial position and adversely impact our stock price.

If any of our product candidates receives marketing approval and we, or others, later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the product could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following undesirable events could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we may be required to recall the product or change the way the product is administered;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we may be required to create a handout, sometimes referred to as a Medication Guide, outlining the risks of the previously unidentified side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients;

- the product may become less competitive; and
- our reputation may suffer.

Any of these events could have a material and adverse effect on our operations and business and could adversely impact our stock price.

Even if one of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, and the market opportunity for the product candidate may be smaller than we estimate.

We have never commercialized a product. Even if one of our product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues and we may not become profitable. The degree of market acceptance of, and potential market opportunity for, our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of the product;
- the potential advantages of the product compared to alternative treatments;
- the prevalence and severity of any side effects;
- the clinical indications for which the product is approved;
- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- our ability to offer the product for sale at competitive prices;
- our ability to establish and maintain pricing sufficient to realize a meaningful return on our investment;
- our ability to prevent use of our INOpulse for PH-COPD device by PAH patients due to expected pricing differences;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- the strength of sales, marketing and distribution support;

- the approval of other new products for the same indications;
- changes in the standard of care for the targeted indications for the product;
- the timing of market introduction of our approved products as well as competitive products and other therapies;
- availability and amount of reimbursement from government payors, managed care plans and other third-party payors;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

The potential market opportunities for our product candidates are difficult to estimate precisely. Our estimates of the potential market opportunities, including our estimates with respect to pricing and reimbursement, are predicated on many assumptions, including industry knowledge and publications, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities.

If we are unable to establish sales, marketing and distribution capabilities or enter into acceptable sales, marketing and distribution arrangements with third parties, we may not be successful in commercializing any product candidates that we develop, if and when those product candidates are approved.

We do not have a sales, marketing or distribution infrastructure and have limited experience in the sale, marketing and distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We expect to build a commercial infrastructure to allow us to market and sell certain of our product candidates when approved, if any, using a specialty sales force in the United States, and we may choose to establish commercialization capabilities in select countries outside the United States. The development of sales, marketing and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. We expect that we will commence the development of these capabilities prior to receiving approval of any of our product candidates. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs. Such a delay may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our product candidates, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

We may partner with third parties to commercialize our product candidates in certain countries outside the United States. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of

them may fail to devote the necessary resources and attention to sell and market our product candidates effectively.

If we do not establish sales and marketing capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates that receive marketing approval.

Even if we are able to commercialize any product candidate that we develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or healthcare reform initiatives that could harm our business.

The commercial success of our product candidates will depend substantially, both in the United States and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish and maintain pricing sufficient to realize a meaningful return on our investment.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs and devices. Marketing approvals, pricing and reimbursement for new drug and device products vary widely from country to country. Some countries require approval of the sale price of a drug or device before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some non-U.S. markets, pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us to decrease the price we might establish for products, which could result in lower than anticipated product revenues. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide adequate coverage or reimbursement, our prospects for revenue and profitability will suffer. Approval of a product does not guarantee sufficient reimbursement to commercialize. For example, assuming positive results, approval of CE marking for BCM in the European Union may be achieved with our ongoing clinical trial but, based on current reimbursement practices in the European Union, this data may not be sufficient to gain sufficient reimbursement for us to invest in commercialization activities.

There may also be delays in obtaining coverage and reimbursement for newly approved products, and coverage may be more limited than the indications for which the product is approved by the FDA or comparable non-U.S. regulatory authorities. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost products or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We cannot be sure that coverage will be available for any product candidate that we commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any our product candidates for which we obtain marketing approval could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

We anticipate that reimbursement of BCM will be based on the patient's diagnosis related group, or DRG, for patients who are covered by Medicare or Medicaid, or through similar reimbursement programs for patients to who are covered by private third-party payors. Within the DRG system, patients are classified by similar diagnoses, which are mapped from the International Statistical Classification of Diseases and Related Health Problems, or ICD, a medical classification list provided by the World Health Organization. The version of ICD that is currently in use with respect to DRG classifications is ICD-9. However, an updated version, ICD-10, has been adopted. We expect that DRG classifications will be required to be mapped against ICD-10 by October 2015 and, as a result, we believe that the DRG classifications will be mapped from ICD-10 rather than ICD-9 at the time we commercialize BCM, if ever, which would result in favorable reimbursement. However, if ICD-9 continues to be used for DRG classification mapping by hospitals or Medicare or Medicaid or other payors, or our expectations with respect to the applicable DRG classification prove incorrect, reimbursement for BCM may prove less favorable or inadequate. In addition, even if ICD-10 is adopted for reimbursement assessments, the mapping to the DRGs, or the amount reimbursed for the DRGs, may change, all of which could adversely affect the ability of our customers to gain sufficient reimbursement, and therefore, the adoption of, or price we could charge for, BCM.

If the FDA or comparable non-U.S. regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

Once an NDA is approved, the product covered thereby becomes a "reference listed drug" in the FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations." Manufacturers may seek approval of generic versions of reference listed drugs through submission of ANDAs in the United States, or through a similar process in foreign jurisdictions. In support of an ANDA, a generic manufacturer need not conduct clinical studies. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference listed drug has expired. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products may face from generic versions of our products could materially and adversely impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on the investments we have made in those product candidates.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

We face an inherent risk of product liability claims as a result of the clinical testing of our product candidates despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we commercially sell any product that we may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. For example:

- improper use or failure of INOpulse may result in rebound pulmonary hypertension, which can be fatal in some patients;
- rebound pulmonary hypertension may also occur if both the primary and back-up devices fail before we can replace them, if the built-in back-up with a device does not work properly or if the patient does not carry or have access to his or her back-up device; and
- rebound pulmonary hypertension can also occur in patients who were not previously considered at risk for this reaction and who may not have been provided an adequate back-up device.

Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for products that we may develop;

- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend resulting litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Although we maintain general liability insurance of $1.0 million in the aggregate, umbrella insurance in the amount of $10.0 million in the aggregate and clinical trial liability insurance of $20.0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we begin the commercial sale of any product candidate that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could adversely affect our business, financial condition, results of operations and prospects.

Our INOpulse devices use lithium-ion battery cells, which have been observed to catch fire or vent smoke and flame, and these events may raise concerns about the batteries we use.

The battery pack used in our INOpulse devices makes use of lithium-ion cells. On rare occasions, lithium-ion cells can rapidly release the energy they contain by venting smoke and flames in a manner that can ignite nearby materials. Highly publicized incidents of laptop computers and cell phones bursting into flames have focused consumer attention on the safety of these cells. There can be no assurance that the battery packs we use would not fail, which could lead to property damage, personal injury or death, and may subject us to lawsuits. We may also have to recall our products, if any, which would be time consuming and expensive. Also, negative perceptions in the healthcare and patient communities regarding the suitability of lithium-ion cells for medical applications or any future incident involving lithium-ion cells could seriously harm our business, even in the absence of an incident involving us.

Risks Related to Our Dependence on Third Parties

The intellectual property underlying INOpulse is exclusively licensed from Ikaria. If Ikaria terminates the license agreement, or fails to prosecute, maintain or enforce the underlying patents, our business will be materially harmed.

We have licensed the intellectual property underlying INOpulse from Ikaria. Despite our best efforts, Ikaria may conclude that we have breached a material term of the license agreement and, as a result, seek to terminate the agreement. In the event the license agreement is terminated, we will lose our ability to market INOpulse, and, upon Ikaria's written request, we will be required to transfer any regulatory approvals that we have obtained for INOpulse to Ikaria.

The license agreement prohibits us from sublicensing to any competitor of Ikaria any intellectual property licensed to us by Ikaria. In addition, we are required to ensure that all of our products, if any, are used solely for the chronic treatment of PAH, PH-COPD and PH-IPF and to enter into written agreements with any

customers that contain restrictions on the use of our products and termination rights in the event such restrictions are violated.

Ikaria has the initial right, but not the obligation, to prosecute and maintain all patents that are licensed to us pursuant to the license agreement. While we have certain step-in rights to assume control if Ikaria declines to file, prosecute or maintain certain licensed patents that are core to our business, in the event Ikaria reasonably determines that our actions could materially impair its business operations or intellectual property rights, Ikaria may prohibit us from taking such actions. In addition, Ikaria has the initial right, but not the obligation, to initiate a legal action against a third party with respect to any actual or suspected infringement of patent rights licensed to us pursuant to the license agreement. We have the right to initiate legal action against a third-party infringer of licensed patents that are core to our business in the event Ikaria declines to take action with respect to such infringement, however, if Ikaria determines that our pursuit of any such action could materially impair its business operations or intellectual property rights, Ikaria may prohibit us from taking any such action.

The license agreement terminates, on an INOpulse product-by-INOpulse product basis, at such time as we are no longer actively and continuously engaged in the development or commercialization of such product. In addition, Ikaria may terminate the license agreement if, among other things, (1) we breach or fail to comply with any material term or condition required to be performed or complied with by us and do not cure such breach or failure within 30 days after receiving written notice of such breach from Ikaria, (2) we or any of our affiliates breaches any of our agreements not to compete with Ikaria, (3) we or any of our affiliates challenges the validity or enforceability of the licensed patents or (4) we or any person that is a successor to our license rights markets a generic nitric oxide product that is competitive with Ikaria's INOmax product. Upon termination of the license agreement with respect to any INOpulse product candidate, we will lose our ability to market such INOpulse product candidate, and upon, Ikaria's written request, be required to transfer any and all regulatory approvals relating to such INOpulse product candidate to Ikaria.

On March 5, 2015, Mallinckrodt and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the license agreement imposes binding obligations on Ikaria to perform in accordance with the license agreement's terms, it is possible that following completion of the sale, as the new owner's influence on Ikaria's operations increases, Ikaria may perform differently under the license agreement than it has to date. Moreover, to the extent that we desire to expand the scope of the license agreement, it is possible that Ikaria will not be willing to do so on reasonable terms, or at all. In any of these circumstances, our business, product development and financial statements could be materially adversely affected.

We rely, and expect to continue to rely, on third parties to conduct our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We currently rely on third-party clinical research organizations, or CROs, to conduct our clinical trials. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. Our agreements with these third parties generally allow the third party to terminate the agreement at any time. If we are required to enter into alternative arrangements because of any such termination, the introduction of our product candidates to market could be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we design our clinical trials and will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. We

also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

We also expect to rely on other third parties to store and distribute drug and device supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential product revenue.

We rely on Ikaria for our supply of nitric oxide for the clinical trials of INOpulse. Ikaria is the sole supplier of nitric oxide. Ikaria's inability to continue manufacturing adequate supplies of nitric oxide, or its refusal to supply us with commercial quantities of nitric oxide on commercially reasonable terms, or at all, could result in a disruption in the supply of, or impair our ability to market, INOpulse.

We have entered into a drug clinical supply agreement with Ikaria, pursuant to which Ikaria will manufacture and supply our requirements for nitric oxide for inhalation and corresponding placebo for use in clinical trials of INOpulse. Ikaria manufactures pharmaceutical-grade nitric oxide at its facility in Port Allen, Louisiana, which is the only FDA-inspected site for manufacturing pharmaceutical-grade nitric oxide in the world. Ikaria's Port Allen facility is subject to the risks of a natural disaster or other business disruption. We maintain under controlled storage conditions a two- to three-month supply of clinical trial drug product, but there can be no assurance that we would be able to meet our requirements for INOpulse if there were a catastrophic event or failure of Ikaria's manufacturing system. Because Ikaria's Port Allen facility is the only FDA-inspected site that can manufacture INOpulse and because the manufacture of a pharmaceutical gas requires specialized equipment and expertise, there are few, if any, third-party manufacturers to which we could contract this work in a short period of time. Therefore, any disruption in Ikaria's Port Allen facility, or the failure by Ikaria for any other reason to provide us with nitric oxide, could materially and adversely affect supplies of INOpulse and our ongoing and planned clinical trials. In addition, we do not currently have any arrangements with Ikaria to provide us with commercial quantities of nitric oxide. If we are unable to arrange for Ikaria to provide such quantities on commercially reasonable terms, or at all, we may not be able to successfully produce and market INOpulse or may be delayed in doing so.

On March 5, 2015, Mallinckrodt and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the drug clinical supply agreement imposes binding obligations on Ikaria to perform in accordance with the agreement's terms, it is possible that following completion of the sale, as the new owner's influence on Ikaria's operations increases, Ikaria may not continue to provide the same level of performance under the drug clinical supply agreement as Ikaria has provided to date. Moreover, to the extent that we desire to expand the scope of the drug clinical supply agreement (to cover commercial quantities of nitric oxide or otherwise), it is also possible that Ikaria will not be willing to do so on reasonable terms, or at all. In any of these circumstances, our business, product development and financial statements could be materially adversely affected.

We rely on third-party suppliers and manufacturers to produce and deliver clinical devices and supplies as well as for the servicing of these devices for our INOpulse product candidate, and may also do so for other product candidates. Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us or to provide necessary servicing may delay or impair our ability to complete our clinical trials.

We currently rely, and expect to continue to rely, on third parties for supply of the device, cannula and certain other supplies for our INOpulse product candidate. These suppliers are, and any future third-party suppliers with whom we enter into agreements may be, our sole suppliers of these devices or any of our other current or future devices used in the INOpulse program. These suppliers are commonly referred to as single-source suppliers. In addition, in February 2015, we entered into an agreement with Flextronics to manufacture and service the Mark2 devices needed for our clinical trials planned in the second half of 2015. If our suppliers fail to deliver materials and provide services needed for the production of the INOpulse device and related supplies or for our other product candidates in a timely and sufficient manner, if they fail to comply with applicable regulations, or if we do not qualify alternate suppliers, clinical development or regulatory approval of our product candidates or commercialization of our products could be delayed, increasing our costs to complete clinical development and to obtain regulatory approval, which could deprive us of potential additional product revenue.

We rely on third-party suppliers and manufacturers to produce and deliver clinical drug supplies for our BCM product candidate and may also do so for other product candidates. Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us may delay or impair our ability to complete our clinical trials.

We currently rely, and expect to continue to rely, on third parties for supply of the ingredients for our BCM product candidate. These suppliers are, and any future third-party suppliers with whom we enter into agreements may be, our sole suppliers of BCM or any of our other current or future product candidates. These suppliers are commonly referred to as single-source suppliers. If our suppliers fail to deliver materials and provide services needed for the production of BCM or our other product candidates in a timely and sufficient manner, if they fail to comply with applicable regulations, or if we do not qualify alternate suppliers, clinical development or regulatory approval of our product candidates or commercialization of our products could be delayed, increasing our costs to complete clinical development and to obtain regulatory approval, which could deprive us of potential additional product revenue.

In addition, we currently outsource the manufacture of BCM for use in clinical trials pursuant to the terms of a manufacturing and supply agreement with a third-party which expires in April 2017. We plan to enter into a manufacturing and supply agreement for BCM with a new third-party manufacturer prior to April 2017. If we fail to enter into a new manufacturing and supply agreement for BCM with a third-party prior to the expiration of our existing manufacturing and supply agreement or if such new agreement is on less favorable terms, our ability to complete our clinical trials for BCM may be impaired.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including reliance on the third party for regulatory compliance and quality assurance, the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control (including a failure to synthesize and manufacture our product candidates in accordance with our product specifications) and the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or damaging to us. In addition, the FDA and other regulatory authorities require that our product candidates be manufactured according to cGMP and similar foreign standards. Any failure by our third-party manufacturers to comply with cGMP or failure to scale up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates. In addition, such failure could be the basis for action by the FDA or other regulatory authorities to withdraw approvals for product candidates previously granted to us and for other regulatory action, including recall or seizure, fines, imposition of operating restrictions, total or partial suspension of production or injunctions.

We rely on our manufacturers to purchase the materials necessary to produce our product candidates for our clinical trials from third-party suppliers. There are a small number of suppliers for certain capital equipment and raw materials that are used to manufacture our product candidates. Such suppliers may not sell these raw materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these raw materials by our manufacturers. Any significant delay in the supply of a product candidate or the raw material components thereof for an ongoing clinical trial due to the need to replace a third-party manufacturer could considerably delay completion or increase the costs of our clinical trials, product testing and potential regulatory approval of our product candidates. If our manufacturers or we are unable to purchase these raw materials after regulatory approval has been obtained for our product candidates, the commercial launch of our product candidates would be delayed or there would be a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates.

We intend to rely on third parties to produce commercial supplies of any approved product candidates. Any failure by a third-party supplier or manufacturer to produce or deliver supplies for us may delay or impair our ability to commercialize our product candidates.

To date, our product candidates have been manufactured in small quantities for pre-clinical studies and clinical trials. If one or more of our product candidates are approved by the FDA or comparable regulatory authorities in other countries for commercial sale, we will need to manufacture such product candidate in larger quantities. We do not currently have any arrangements with Ikaria or another third-party manufacturer to provide commercial quantities of our product candidates. If we are unable to arrange for such a third-party manufacturing source, or fail to do so on commercially reasonable terms, we may not be able to successfully produce and market our product candidates or may be delayed in doing so.

If we successfully commercialize any of our product candidates, we may be required to establish or access large-scale commercial manufacturing capabilities. We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we currently have no plans to build our own clinical or commercial scale manufacturing capabilities.

Our BCM product candidate currently in development is exclusively licensed from BioLineRx Ltd., and we may enter into additional agreements to in-license technology from third parties. If BioLineRx Ltd. or other future licensors terminate the applicable license, or fail to maintain or enforce the underlying patents, our competitive position and market share will be harmed.

We have an exclusive worldwide license for our BCM product candidate, subject to certain retained rights of the licensor, from BioLine. Under the terms of the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize at least one product containing BCM. BioLine has the right to terminate its license agreement with us for an uncured material breach by us, upon which our exclusive license for BCM will terminate.

We have also exclusively licensed INOpulse, for certain indications and settings, and subject to certain retained rights of the licensor, from Ikaria. See “Certain Relationships and Related Person Transactions—Relationship with Ikaria” for a summary of our exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria.

We may enter into additional license agreements as part of the development of our business in the future. Such licensors, if any, may be responsible for prosecution of certain patent applications and maintenance of certain patents. Such licensors may not successfully prosecute such patent applications or maintain such patents, which we have licensed and on which our business depends. Our licensors may fail to pursue litigation against third-party infringers, may fail to prove infringement, or may fail to defend against counterclaims of patent invalidity or unenforceability. If these in-licenses are terminated, or if the underlying patents fail to provide the intended market exclusivity, competitors would have the freedom to seek regulatory approval of,

and to market, products identical to ours. This could have a material adverse effect on our competitive business position and our business prospects.

We may have received better terms from unaffiliated third parties than the terms we received in our agreements with Ikaria.

The agreements related to the Spin-Out, including the separation and distribution agreement, TSA, license agreement, drug clinical supply agreement, device clinical supply agreement, agreements not to compete and the other agreements, were negotiated in the context of our separation from Ikaria while we were still part of Ikaria and, accordingly, may not reflect terms that would have resulted from arm's-length negotiations among unaffiliated third parties. The terms of the agreements we negotiated in the context of our separation related to, among other things, allocation of assets, liabilities, rights, indemnifications and other obligations among Ikaria and us. We may have received better terms from third parties because third parties may have competed with each other to win our business. Some of our board members are also members of the Ikaria board. See "Certain Relationships and Related Person Transactions—Relationship with Ikaria."

Third parties may seek to hold us responsible for liabilities of Ikaria that we did not assume in our agreements.

In connection with our separation from Ikaria, Ikaria has generally agreed to retain all liabilities that did not historically arise from our business. Third parties may seek to hold us responsible for Ikaria's retained liabilities. Under our agreements with Ikaria, Ikaria has agreed to indemnify us for claims and losses relating to these retained liabilities. However, if those liabilities are significant and we are ultimately liable for them, we cannot assure our stockholders that we will be able to recover the full amount of our losses from Ikaria.

Any disputes that arise between us and Ikaria with respect to our past and ongoing relationships could harm our business operations.

Disputes may arise between Ikaria and us in a number of areas relating to our past and ongoing relationships, including:

- intellectual property, technology and business matters, including failure to make required technology transfers and failure to comply with non-compete provisions applicable to Ikaria and us;
- labor, tax, employee benefit, indemnification and other matters arising from our separation from Ikaria;
- distribution and supply obligations;
- employee retention and recruiting;
- business combinations involving us;
- the nature, quality and pricing of transitional services Ikaria has agreed to provide us; and
- business opportunities that may be attractive to both Ikaria and us.

We may not be able to resolve any potential conflicts, and even if we do, the resolution may be less favorable than if we were dealing with an unaffiliated party.

We may seek to enter into collaborations with third parties for the development and commercialization of our product candidates. If we fail to enter into such collaborations, or such collaborations are not successful, we may not be able to capitalize on the market potential of our product candidates.

We may seek third-party collaborators for development and commercialization of our product candidates. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical and medical device companies, regional and national biotechnology companies and pharmaceutical companies. We are not currently party to any such arrangement. However, if we do enter into any such arrangements with any third parties in the future, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates would pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators with marketing and distribution rights to one or more of our products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

If we are not able to establish collaborations, we may have to alter our development and commercialization plans.

Our drug and device development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with biotechnology and pharmaceutical companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of our current or future license agreements may restrict our ability to enter into agreements on certain terms with future collaborators. For example, our license agreement with Ikaria prohibits us from granting a sublicense under any of the intellectual property licensed to us under such license agreement to any of our affiliates or any third party, in each case, that directly or indirectly competes with the Ikaria nitric oxide business, and any future license agreements may contain similar restrictions. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and products. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates. The patents we have licensed from Ikaria relating to INOpulse's feature of providing delivery of nitric oxide to ensure a consistent dose over time expire as late as 2027 in the United States and as late as 2026 in certain other countries, as well as a patent with respect to the triple-lumen cannula that allows for safer and more accurate dosing of pulsed inhaled nitric oxide, which expires in 2033. The patents we have licensed from BioLine relating to our BCM product candidate expire as late as 2029 in the United States, with a possible patent term extension to 2032 to 2034, and 2024 in certain other countries.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, pursuant to our license agreement with Ikaria, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering the INOpulse technology that we license from Ikaria, except in the event that Ikaria declines to prosecute or maintain certain licensed patents that are core to our business, elects to allow any of such patents to lapse or elects to abandon any such patents, in which case we would have step-in rights to assume control of the prosecution and/or maintenance of such patents, subject to Ikaria's right to prohibit us from taking such actions if it reasonably determines that such actions could materially impair its business, operations or intellectual property rights. Similarly, under the terms of any future agreements that we may enter into with other third parties, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering the technology that is licensed to us under such agreements. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of non-U.S. countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, and in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not issue as patents that protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our owned or licensed issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. The Leahy-Smith Act includes provisions that affect the way patent applications are prosecuted and affect patent litigation. The USPTO recently developed new regulations and procedures to govern administration of the Leahy-Smith Act. Many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or licensed patent applications and the enforcement or defense of our owned or licensed issued patents, all of which could have a material adverse effect on our business and financial condition.

Moreover, we may be subject to third-party preissuance submissions of prior art to the USPTO, or become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging our owned or licensed patent rights or the patent rights of others. For example, Notices of Opposition to two European patents covering BCM that we licensed from BioLine have been filed with the European Patent Office. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection

provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us, or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. We may not receive patent term extension under the Hatch-Waxman Act that we expect or our rights during the extension period may be more limited than the full scope of the patent, making it easier for our competitors to develop and market non-infringing technologies or products.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate, or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our owned or licensed patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file or participate in infringement claims, which can be expensive and time consuming. Any claims we or our licensors assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours or our licensor is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our owned or licensed patents at risk of being invalidated or interpreted narrowly.

Under the terms of our license agreement with Ikaria, in the event a third party is suspected of infringing any patent rights licensed to us by Ikaria, Ikaria has the initial right, but not the obligation, to initiate a legal action against such third party. In the event that Ikaria declines to take any action with respect to an alleged infringement of certain licensed patents that are core to our business, we have the right, in certain circumstances, to initiate a legal action against such third party, provided that, if Ikaria reasonably determines that our pursuit of any action with respect to infringement of any of such core patents could materially impair Ikaria's business operations or intellectual property rights, Ikaria may require us to not undertake or to cease any such action. Our inability to initiate a legal action against a third party suspected of infringing intellectual property rights important to our business may have a material adverse effect on our competitive business position and our business prospects.

If we fail to comply with our obligations under license agreements, we could lose rights that are important to our business.

We are party to a license agreement with BioLine relating to our BCM product candidate that imposes, and we may enter into additional license agreements that may impose, various diligence, milestone payment, royalty and other obligations on us. Under our existing license agreement with BioLine, we are obligated to pay royalties on the net sales of product candidates or related technologies to the extent they are covered by the agreement. We also have diligence and development obligations under this agreement. Moreover, under our license agreement with Ikaria, we have granted Ikaria a sole and exclusive worldwide license to any intellectual property rights that we control for use in Ikaria's nitric oxide business, are required to ensure that all of our products, if any, are used solely for the chronic treatment of PAH, PH-COPD and PH-IPF and to enter into written agreements with any customers that contain restrictions on the use of our products and termination rights in the event such restrictions are violated, and have agreed to pay 100% of the reasonable and documented costs incurred by Ikaria for the prosecution and maintenance of certain licensed patents that are core to our business and 10% of such costs incurred by Ikaria for all other licensed patents. If we fail to comply with our obligations under current or future license agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product that is covered by the agreement or face other penalties under the agreement. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement.

For example, BioLine recently indicated to us that it believed that we had breached our license agreement in several ways. We were able to reach agreement with BioLine and resolve the dispute through an amendment to the license agreement that includes a release of claims by BioLine. However, had we not been able to reach resolution and had BioLine brought and prevailed in a lawsuit against us, one of the potential remedies could have been the termination of the license agreement and our consequent loss of rights to BCM. Termination of our license agreement with BioLine, or any future license agreements we may enter into, or reduction or elimination of our rights under such agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the pharmaceutical, biotechnology and medical device industries. We may become party to, or be threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our products and technology, including interference or derivation proceedings before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims by third parties asserting that we or our employees have misappropriated their intellectual property, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at other pharmaceutical, biotechnology or medical device companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in timely obtaining such an agreement with each party who in fact develops intellectual property that we regard as our own. Even if timely obtained, such agreements may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

If we fail in prosecuting or defending any such claims, we may lose valuable intellectual property rights or personnel, in addition to paying monetary damages. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Even if we are successful in prosecuting such claims, any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- Others may be able to develop and commercialize treatments that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed.
- We or our licensors might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed.
- We or our licensors might not have been the first to file patent applications covering certain of our inventions.
- Others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.

- It is possible that our pending patent applications will not lead to issued patents.
- Issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors.
- Our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.
- We may not develop additional proprietary technologies that are patentable.
- The patents of others may have an adverse effect on our business.
- Another party may be granted orphan exclusivity for an indication that we are seeking before us or may be granted orphan exclusivity for one of our products for another indication.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary clinical trials, the marketing approval process is expensive, time consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and similar regulatory authorities outside the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. Our product candidates are in the early stages of development and are subject to the risks of failure inherent in drug and device development. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in conducting and managing the clinical trials, and in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing marketing approval requires the submission of extensive pre-clinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional pre-clinical, clinical or other studies. In addition, varying interpretations of the data obtained from pre-clinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. If we experience delays

in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad, and any approval we are granted for our product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market and sell our products in the European Union and many other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Even if we obtain marketing approval for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation, including the requirement to implement a risk evaluation and mitigation strategy or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. In addition, manufacturers of approved products and those manufacturers' facilities are required to ensure that quality control and manufacturing procedures conform to cGMP, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our contract manufacturers could be subject to periodic unannounced inspections by the FDA and other regulatory authorities to monitor and ensure compliance with cGMP.

Accordingly, assuming we receive marketing approval for one or more of our product candidates, we and our contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Thus, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any product candidate for which we obtain marketing approval will be subject to strict enforcement of post-marketing requirements and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include, but are not limited to, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping.

The FDA and other federal and state agencies, including the Department of Justice, closely regulate compliance with all requirements governing prescription drug and device products, including requirements pertaining to marketing and promotion of drugs and devices in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. Violations of such requirements may lead to investigations alleging violations of the Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act and other federal and state health care fraud and abuse laws as well as state consumer protection laws. Our failure to comply with all regulatory requirements, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

- litigation involving patients taking our products;
- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- untitled or warning letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or

- injunctions or the imposition of civil or criminal penalties.

Non-compliance by us or any future collaborator with regulatory requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;

- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal government program, or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, requires applicable manufacturers of covered drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals and physician ownership and investment interests; and

- analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and non-U.S. laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates and products outside of the United States and require us to develop and implement costly compliance programs.

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or the FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third party in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the medical device industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain product candidates and products outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or the SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

Currently, we do not operate any research and development or production facilities, including laboratory, development or manufacturing facilities. However, if we decided to operate our own research and development and production facilities, we would be subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Such operations may involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and wastes, we would not be able to eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use or disposal of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we would increase our level of workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not expect to maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our possible future storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are dependent on the scientific, business development and clinical expertise of our management team, including Jonathan Peacock, our chief executive officer, Manesh Naidu, our chief business officer, Reinilde Heyrman, our chief clinical development officer, and Martin Meglasson, our chief scientific officer. We recently hired our chief executive officer. Leadership transitions can be inherently difficult to manage and may cause some disruptions in our business.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. Any of our employees may terminate their employment with us at any time. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. We do not maintain "key person" insurance for any of our executives or other employees. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical, biotechnology and medical device companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data accurately, to disclose unauthorized activities to us or to comply with our code of business conduct and ethics. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, false claims, inappropriate promotion, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

In addition, during the course of our operations, our directors, executives and employees may have access to material, non-public information regarding our business, our results of operations or potential transactions we are considering. We may not be able to prevent a director, executive or employee from violating our insider trading policies and trading in our common stock on the basis of, or while having access to, material, non-public information. If a director, executive or employee was to be investigated, or an action was to be brought against a director, executive or employee for insider trading, it could have a negative impact on our

reputation and our stock price. Such a claim, with or without merit, could also result in substantial expenditures of time and money, and divert attention of our management team from other tasks important to the success of our business.

We expect to expand our development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of December 31, 2014, we had 48 full-time employees, of which 41 employees were engaged in research and development. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of development, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to Ownership of Our Common Stock

Our principal stockholders have substantial control over us, which could limit ability of our stockholders to influence the outcome of key transactions, including any change of control.

Our executive officers, directors and stockholders who are known by us to beneficially own more than 5% of our common stock, in the aggregate, beneficially owned 77.4% our outstanding common stock as of March 16, 2015. As a result, if these stockholders were to choose to act together, they would be able to exert a significant degree of influence over matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, could delay, defer or prevent a change in control; entrench our management or board of directors; or impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

In addition, as of March 16, 2015, our largest stockholder, investment funds affiliated with New Mountain Capital, or the New Mountain Entities, owned, in the aggregate, approximately 37.7% of our outstanding common stock. Pursuant to the terms of a stockholders agreement, the New Mountain Entities is entitled to designate one director for nomination to our board of directors and to designate one director to the board of directors (or equivalent governing body) of each of our subsidiaries and to appoint the lead director of our board of directors, in each case, for so long as the New Mountain Entities or certain of their respective assignees beneficially own (i) 50% or more of the sum of (a) the aggregate number of shares of our common stock that they collectively owned immediately prior to the closing of our initial public offering and (b) the number of shares of our common stock, if any, acquired following the closing of our initial public offering and (ii) 15% or more of our common stock outstanding (as set forth on the cover of our then most recently filed annual report on Form 10-K or quarterly report on Form 10-Q).

The New Mountain Entities also have certain other rights conferred by the stockholders agreement. The New Mountain Entities may exert significant influence over matters requiring board approval. In addition, their consent is required for certain matters requiring approval by our stockholders, including the compensation and hiring and firing of our chief executive officer, business combinations, issuance of shares of our capital stock and incurrence of debt. These stockholder approval rights will terminate when the New Mountain Entities own either (i) less than 50% of the sum of (a) the number of shares of our common stock that they collectively owned immediately prior to the closing of our initial public offering and (b) the number of shares of our common stock,

if any, acquired following the closing of our initial public offering or (ii) less than 15% of our common stock outstanding (as set forth on the cover of our then most recently filed annual report on Form 10-K or quarterly report on Form 10-Q).

Our second largest stockholder, Linde North America, Inc., an indirect wholly-owned subsidiary of Linde AG, or Linde, owned approximately 12.6% of our outstanding common stock. Pursuant to the terms of a stockholders agreement, Linde is entitled to designate one director to our board of directors and to designate one director to the board of directors (or equivalent governing body) of each of our subsidiaries, in each case, for so long as Linde and/or certain of its assignees beneficially own (i) 50% or more of the sum of (a) the aggregate number of shares of our common stock that they collectively owned immediately prior to the closing of our initial public offering and (b) the number of shares of our common stock, if any, acquired following the closing of our initial public offering and (ii) 10% or more of our common stock outstanding (as set forth on the cover of our then most recently filed annual report on Form 10-K or quarterly report on Form 10-Q).

The New Mountain Entities and Linde may have interests that differ from the interests of our other stockholders, and they may vote in ways with which our other stockholders disagree and that may be adverse to interests of our other stockholders. The concentration of ownership of our capital stock may have the effect of delaying, preventing or deterring a change of control of our company, could deprive our stockholders of an opportunity to receive a premium for their common stock as part of a sale of our company and may adversely affect the market price of our common stock.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is performing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. As of March 16, 2015, we had outstanding 12,905,392 shares of common stock. This includes the 5,000,000 shares that we sold in our initial public offering, which may be resold in the public market immediately without restriction, unless purchased by our affiliates. The remaining 7,905,392 shares currently are restricted as a result of securities laws or lock-up agreements entered into in connection with our initial public offering but will be able to be sold into the public market in the near future. Moreover, as of March 16, 2015, holders of an aggregate of approximately 8,733,628 shares of our common stock have rights, subject to certain conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. In February 2015, we filed a registration statement registering all shares of common stock that we may issue under our equity compensation plans. As of March 16, 2015, we had outstanding options to purchase an aggregate of 1,333,047 shares of our common stock, of which options to purchase approximately 689,906 were vested. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements entered into in connection with our initial public offering.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price or trading volume of our stock could decline.

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. If no, or few, analysts commence coverage of us, the trading price of our stock would likely decrease. Even if we do obtain analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price or trading volume to decline.

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for our stockholders.

Our stock price may be volatile. The stock market in general, and the market for pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their shares of common stock at or above the price they paid for their shares. The market price for our common stock may be influenced by many factors, including:

- actual or anticipated results from and any delays in our clinical trials, including our expected and ongoing clinical trials of our INOpulse and BCM product candidates, as well as results of regulatory input on our clinical trial programs and regulatory reviews relating to the approval of our product candidates;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- failure or discontinuation of any of our clinical development programs;
- the level of expenses related to any of our product candidates or clinical development programs;
- commencement or termination of any collaboration or licensing arrangement;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures and capital commitments;
- additions or departures of key scientific or management personnel;
- variations in our financial results or those of companies that are perceived to be similar to us;
- new products, product candidates or new uses for existing products introduced or announced by our competitors, and the timing of these introductions or announcements;
- results of clinical trials of product candidates of our competitors;
- general economic and market conditions and other factors that may be unrelated to our operating performance or the operating performance of our competitors, including changes in market valuations of similar companies;
- regulatory or legal developments in the United States and other countries;
- changes in the structure of healthcare payment systems;
- conditions or trends in the pharmaceutical, biotechnology and medical device industries;
- actual or anticipated changes in earnings estimates, development timelines or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;

- sales of common stock by us or our stockholders in the future, as well as the overall trading volume of our common stock; and
- the other factors described in this "Risk Factors" section.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

An active trading market for our common stock may not be sustained.

Our shares of common stock began trading on the NASDAQ Global Market on February 13, 2015. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares may not continue to develop or be sustained. If an active market for our common stock does not continue to develop or is not sustained, it may be difficult for investors to sell shares without depressing the market price for the shares, or at all.

We have broad discretion in the use of our cash and cash equivalents and may not use them effectively.

Our management will have broad discretion in the application of our cash and cash equivalents and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earlier of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) December 31, 2020; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the first day of the year following the first year in which the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this Annual Report on Form 10-K. In particular, we have not included all of the executive compensation information that would be required if we were not an emerging growth company. We cannot predict whether investors will find our common stock less attractive if we rely on certain or all of these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are currently incurring and expect to continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a newly public company, we are incurring and expect to continue to incur significant legal, accounting and other expenses that we did not incur as a private company. We expect that these expenses will further increase after we are no longer an "emerging growth company." We expect that we will need to hire additional accounting, finance and other personnel to comply with the requirements of being a public company, and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and NASDAQ have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance. Overall, we estimate that our incremental costs resulting from operating as a public company may be between $2.0 million and $4.0 million per year, which costs are in addition to our expected incremental costs resulting from operating as a stand-alone company.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. We became a stand-alone company in February 2014 following the Spin-Out and, as such, have a very limited operating history. Accordingly, many of the internal controls over financial reporting have only recently been implemented and therefore have not been tested. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Our certificate of incorporation provides that the doctrine of "corporate opportunity" will not apply to any of our stockholders or directors, except in limited circumstances, which may adversely affect our business or prospects.

Our certificate of incorporation provides that the doctrine of "corporate opportunity" will not apply to any of our stockholders or directors, other than any stockholder or director that is an employee of ours. The doctrine of corporate opportunity generally provides that a corporate fiduciary may not develop an opportunity using corporate resources, acquire an interest adverse to that of the corporation or acquire property that is reasonably incident to the present or prospective business of the corporation or in which the corporation has a present or expectancy interest, unless that opportunity is first presented to the corporation and the corporation chooses not to pursue that opportunity. The doctrine of corporate opportunity is intended to preclude officers or directors from personally benefiting from opportunities that belong to the corporation. We have renounced any prospective corporate opportunity so that our stockholders and directors (other than those that are employees of ours) and their respective representatives have no duty to communicate or present corporate opportunities to us, including any opportunity that becomes known to Ikaria and its directors, and have the right to either hold any corporate opportunity for its (and its representatives') own account and benefit or to recommend, assign or otherwise transfer such corporate opportunity to persons other than us, including to Ikaria. As a result, our stockholders, directors and their respective affiliates will not be prohibited from investing in competing businesses or doing business with our customers. Therefore, we may be in competition with our stockholders, directors or their respective affiliates, and we may not have knowledge of, or be able to pursue, a transaction that could potentially be beneficial to us. Accordingly, we may lose a corporate opportunity or suffer competitive harm, which could negatively impact our business or prospects.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine. This provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find this provision in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Provisions in our certificate of incorporation, our bylaws or Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the trading price of our common stock.

Provisions of our certificate of incorporation, our bylaws or Delaware law may discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions may also prevent or frustrate attempts by our stockholders to change the composition of our board of directors or to replace or remove our management. These provisions include:

- limitations on the removal of directors;
- a classified board of directors so that not all members of our board are elected at one time;

- advance notice requirements for stockholder proposals and nominations;
- limitations on the ability of stockholders to call and bring business before special meetings and to take action by written consent in lieu of a meeting;
- limitations on the liability of, and the provision of indemnification to, our director and officers; and
- the ability of our board of directors to authorize the issuance of blank check preferred stock, which could be issued with voting, liquidation, dividend and other rights similar to our common stock.

In addition, we are subject to Section 203 of the Delaware General Corporation Law, which prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

The existence of the foregoing provisions and anti-takeover measures could limit the price that investors might be willing to pay in the future for shares of our common stock. They could also deter potential acquirers of our company, thereby reducing the likelihood that investors could receive a premium for their shares of our common stock in an acquisition.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be the sole source of gain for our stockholders.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our principal facilities consist of approximately 25,000 square feet of office space at Ikaria's headquarters located in Hampton, New Jersey and approximately 3,200 square feet of office space and research lab facilities at the Commercialization Center for Innovative Technologies located in North Brunswick, New Jersey. We have access to the office space at Ikaria's headquarters until February 2016, pursuant to the TSA. We lease the space in North Brunswick, New Jersey under a lease that expires in March 2016.

Item 3. Legal Proceedings

We are not presently a party to any material litigation or regulatory proceeding, and we are not aware of any pending or threatened litigation or regulatory proceeding against us that could have a material adverse effect on our business, operating results, financial condition or cash flows.

Item 4. Mine Safety Disclosures

None.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock has been publicly traded on the NASDAQ Global Market under the symbol "BLPH" since February 13, 2015. Prior to that time, there was no public market for our common stock. As a result, we have not set forth quarterly information with respect to the high and low sales prices for our common stock for the two most recent fiscal years. The following table sets forth the high and low sales prices per share for our common stock on the NASDAQ Global Market from February 13, 2015, our first day of trading on NASDAQ, to March 25, 2015:

2015	High	Low
First Quarter (February 13, 2015 through March 25, 2015)	$ 12.92	$ 8.01

Holders

As of March 25, 2015, there were approximately 258 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividend Policy

We have not declared or paid any cash dividends on our common stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future.

Information About Our Equity Compensation Plans

Information regarding our equity compensation plans is incorporated by reference to Item 12, "Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters—Equity Compensation Plan Information" of Part III of this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

Set forth below is information regarding shares of common stock issued, and options and restricted stock units, or RSUs, granted, by us during 2014 and prior to our initial public offering in February 2015 that were not registered under the Securities Act of 1933, as amended, or the Securities Act. Included is the consideration, if any, we received for such shares, options and RSUs and information relating to the section of the Securities Act or rule of the SEC under which exemption from registration was claimed.

On February 9, 2014, we, Ikaria and Ikaria Acquisition Inc. entered into a separation and distribution agreement which provided for and contained the key terms of our separation from Ikaria, which we refer to as the Spin-Out. Prior to the Spin-Out, we issued to certain employees and directors of ours or of our then parent company, Ikaria, and certain accredited investors, options to purchase an aggregate of 618,212 of our non-voting units, at a weighted average exercise price of $7.24 per unit. Between February 10, 2014 and February 12, 2015, we issued to certain employees options to purchase an aggregate of 514,266 of our non-voting units, at a weighted average exercise price of $13.28 per unit.

Prior to the Spin-Out, in February 2014, we issued to certain employees and directors of ours or of Ikaria and certain accredited investors RSUs in respect of an aggregate of 372,947 of our non-voting units,

which we refer to as the Bellerophon RSUs. We subsequently settled such Bellerophon RSUs by issuing and delivering an aggregate of 372,947 non-voting units to the holders of Bellerophon RSUs.

In February 2015, prior to our initial public offering, we issued and sold 67 non-voting units to Mr. Peacock, our president and chief executive officer, at a price per unit of $15.03 for an aggregate purchase price of $1,007.

Prior to our initial public offering, we converted from a Delaware limited liability company into a Delaware corporation. In connection with the conversion, all of our outstanding voting units and non-voting units converted into shares of voting common stock and non-voting common stock, respectively, and options to purchase our non-voting units became options to purchase non-voting shares of our common stock. Pursuant to their terms, upon the consummation of our initial public offering, the non-voting common stock converted into voting common stock and options to purchase non-voting common stock became options to purchase voting common stock.

Each of the foregoing issuances was made by us in a transaction not involving a public offering pursuant to an exemption from the registration requirements of the Securities Act in reliance upon Section 4(a)(2) of the Securities Act or Rule 701 promulgated under Section 3(b) of the Securities Act. We did not pay or give, directly or indirectly, any commission or other remuneration, including underwriting discounts or commissions, in connection with any of the issuances of securities listed above, and no underwriters were involved in the foregoing issuances of securities. All recipients either received adequate information about the registrant or had access, through employment or other relationships, to such information.

Use of Proceeds

We effected the initial public offering of our common stock through a Registration Statement on Form S-1 (File No. 333-201474) that was declared effective by the SEC on February 13, 2015. On February 19, 2015, we completed the sale of 5,000,000 shares of common stock in our initial public offering at a price to the public of $12.00 per share, resulting in net proceeds to us of $52.6 million, after deducting underwriting discounts and commissions of $4.2 million and offering costs of $3.2 million. In addition, we granted the underwriters a 30-day option to purchase up to 750,000 additional shares of common stock at the initial public offering price to cover over allotments, if any. The offering commenced on February 13, 2015 and terminated before the sale of all of the securities registered in the offering. None of the underwriting discounts and commissions or other offering expenses were paid to directors or officers of ours or their associates or to persons owning 10% or more of our common stock or to any affiliates of ours. Leerink Partners LLC and Cowen and Company, LLC acted as joint book-running managers of the offering and as representatives of the underwriters. SunTrust Robinson Humphrey, Inc. and FBR Capital Markets & Co. acted as co-managers for the offering. There were no selling stockholders in the offering.

None of the net proceeds were paid directly or indirectly to directors or officers of ours or their associates or to persons owning 10% or more of our common stock or to any affiliates of ours, other than payments in the ordinary course of business to officers for salaries and to non-employee directors as compensation for board or board committee service. We have invested the net proceeds from the offering in a variety of capital preservation investments, including short-term, interest bearing, investment grade securities. There has been no material change in our planned use of the balance of the net proceeds from the offering as described in our final prospectus filed with the SEC pursuant to Rule 424(b) under the Securities Act.

Item 6. Selected Financial Data

The following selected financial data should be read together with our financial statements and the related notes appearing elsewhere in this Annual Report on Form 10-K and the "Management's Discussion and Analysis of Financial Condition and Results of Operations" section of this Annual Report on Form 10-K. We have derived the statements of operations and comprehensive loss data for the years ended December 31, 2014, 2013 and 2012 and the balance sheet data as of December 31, 2014 and 2013 from our audited financial statements included elsewhere in this Annual Report on Form 10-K, which have been audited by KPMG LLP, an independent registered public accounting firm. The balance sheet data as of December 31, 2012 are from our audited financial statements that are not included in this Annual Report on Form 10-K. Our historical results for any prior period are not necessarily indicative of results to be

expected in any future period.

(in thousands, except per unit data)	Year Ended December 31, 2014	2013	2012
Statement of Operations and Comprehensive Loss Information			
Operating expenses:			
Research and development	$ 45,978	$ 52,985	$ 38,727
General and administrative	13,775	9,013	7,185
Other operating expense	—	—	315
Total operating expenses	59,753	61,998	46,227
Other expense (income)	(79)	—	—
Net loss and comprehensive loss	$ (59,674)	$ (61,998)	$ (46,227)
Net loss per unit:			
Basic and diluted (1)	$ (7.56)		

(in thousands)	As of December 31, 2014	2013	2012
Balance Sheet Information			
Cash and cash equivalents	$ 16,815	$ —	$ —
Restricted cash, current	9,264	—	—
Restricted cash, non-current	1,548	—	—
Working capital (deficit)	17,227	(12,440)	(10,892)
Total assets	33,391	3,636	3,349
Allocated portion of Ikaria special dividend bonus payable, non-current	—	4,273	2,865
Other non-current liabilities	—	1,108	389
Total long term liabilities	—	5,381	3,254
Investment by Ikaria, Inc.	—	160,778	103,401
Members' capital	77,156	—	—
Accumulated deficit	(54,219)	(176,515)	(114,517)
Members' equity / invested (deficit)	$ 22,937	$ (15,737)	$ (11,116)

(1) The weighted average units outstanding for basic and diluted net loss per unit for the year ended December 31, 2014 is 7,898,289. No net loss per unit information is presented for periods prior to the Spin-Out.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our financial condition and results of operations should be read together with our financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties and should be read together with the "Risk Factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

Business

We are a clinical-stage therapeutics company focused on developing innovative products at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary and cardiac diseases. We have two programs in advanced clinical development. The first program, INOpulse, is based on our proprietary pulsatile nitric oxide delivery device. We are currently developing two product candidates under our INOpulse program: one for the treatment of pulmonary arterial hypertension, or PAH, for which we intend to commence Phase 3 clinical trials in the second half of 2015, and the other for the treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease, or PH-COPD, which is in Phase 2 development. Our second program is bioabsorbable cardiac matrix, or BCM, which is currently in a placebo-controlled clinical trial designed to support CE mark registration in the European Union. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure, and we expect to report top line results in mid-2015. Assuming positive results from this trial, we intend to conduct a pivotal pre-market approval trial of BCM beginning in the first half of 2016, which will be designed to support registration in the United States. We are developing BCM for the prevention of cardiac remodeling, which often leads to congestive heart failure following an ST-segment elevated myocardial infarction, or STEMI.

We have devoted substantially all of our resources to our drug discovery and development efforts, including conducting clinical trials for our product candidates, protecting our intellectual property and the general and administrative support of these operations. We have devoted significant time and resources to developing and optimizing our drug delivery system, INOpulse, which operates through the administration of nitric oxide as brief, controlled pulses that are timed to occur at the beginning of a breath. In addition, we have incurred significant costs to scale up manufacturing for BCM from pre-clinical studies to clinical trials.

To date, we have generated no revenue from product sales. We expect that it will be several years before we commercialize a product candidate, if ever.

Separation and Spin-Out from Ikaria

Prior to February 2014, we were a wholly-owned subsidiary of Ikaria. As part of an internal reorganization of Ikaria in October 2013, Ikaria transferred to us exclusive worldwide rights, with no royalty obligations, to develop and commercialize pulsed nitric oxide in PAH, PH-COPD and pulmonary hypertension associated with idiopathic pulmonary fibrosis, or PH-IPF. Following the internal reorganization, in February

2014, Ikaria distributed all of our then outstanding units to its stockholders through the payment of a special dividend on a pro rata basis based on each stockholder's ownership of Ikaria capital stock, which we refer to as the Spin-Out, and as a result we became a stand-alone company.

Our inception date is August 26, 2009, which is the date that BCM was licensed to us by BioLine. Our operations since that date have included organization and staffing, business planning, in-licensing technology, developing product candidates in clinical programs, evaluating potential future product candidates, as well as undertaking pre-clinical studies and clinical trials of our product candidates.

We are in the process of developing and implementing plans to replace services currently provided to us by Ikaria under the TSA and the 2015 Services Agreement. These services include, among others, accounting and financial management support, human resources support, drug and device safety services, biometrics support, information technology services and manufacturing and device servicing support. We expect the costs related to replacing the services currently provided by Ikaria under the TSA will be approximately the same as the $772,000 per month that we are currently paying under the TSA, and we expect the costs related to replacing the services currently provided by Ikaria under the 2015 Services Agreement will be approximately the same as the amounts we are paying under the 2015 Services Agreement. However, although we believe our estimates are reasonable based on the information we have to date, certain significant components of our estimates are preliminary and subject to change.

Accounting for the Separation and Spin-Out

Our historical financial statements for periods prior to February 12, 2014, the date of the Spin-Out, included in this Annual Report on Form 10-K and discussed in this Management's Discussion and Analysis of Financial Condition and Results of Operations were derived from the audited historical financial statements and accounting records of Ikaria and include allocations for direct costs and indirect costs attributable to the research and development segment of Ikaria. In particular, for periods prior to February 12, 2014, our financial statements include expense allocations for (1) certain corporate functions historically provided by Ikaria, including finance, audit, legal, information technology and human resources services, (2) research and development expenses and (3) stock-based compensation. These allocations are based on either specific identification or allocation methods such as time and wage studies, headcount or other measures determined by us. Management believes that the statements of operations for periods prior to the Spin-Out include a reasonable allocation of costs and expenses incurred by Ikaria from which we benefited. See Notes 1 and 2 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Our balance sheet as of December 31, 2013 includes assets and liabilities of Ikaria that were identified as specifically attributable to our INOpulse and BCM product candidates and those that were allocated from Ikaria to us based on an estimate of the benefit derived by us from the underlying asset or liability. Ikaria historically used a centralized approach to cash management and financing of its operations. Cash transfers to us have been accounted for as a capital contribution from Ikaria.

Due to this presentation, the financial information included in this Annual Report on Form 10-K does not reflect what our financial position, results of operations and cash flows will be in the future or what our financial position, results of operations and cash flows would have been in the past had we been a public, stand-alone company during the periods presented.

Financial Position and Outlook

Since inception, we have never been profitable and have incurred significant operating losses. Our net losses were $59.7 million, $62.0 million and $46.2 million for the years ended December 31, 2014, 2013 and 2012, respectively. As of December 31, 2014, our sole source of funding was investments in us by our former parent company, Ikaria.

On February 19, 2015, we completed the sale of 5,000,000 shares of common stock at a price to the public of $12.00 per share, resulting in net proceeds to us of $52.6 million after deducting underwriting discounts and commissions of $4.2 million and offering costs of $3.2 million.

We expect to continue to incur significant expenses and operating losses for the foreseeable future as we continue the development and clinical trials of, and seek regulatory approval for, our product candidates. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses. We do not currently have the infrastructure for the sale, marketing, manufacture and distribution of any products. To develop a commercial infrastructure, we will have to invest financial and management resources, some of which would have to be deployed prior to having any certainty of marketing approval.

We have entered into license agreements with Ikaria and BioLine pursuant to which we obtained rights to our product candidates. In the future, we may enter into additional licensing agreements for new product candidates or strategic or co-promotion agreements with partners for the development and/or commercialization of product candidates in the United States or other countries.

We are currently incurring and expect to continue to incur additional costs associated with operating as a public company. Unless and until we generate sufficient revenue to be profitable, we will seek to fund our operations primarily through public or private equity or debt financings or other means, which may include strategic partnerships with third parties in the United States or other countries with respect to certain or all of our programs. Other additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed could have a material adverse effect on our business, results of operations, financial condition, cash flows and future prospects.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the next several years, if ever. In the future, we may generate revenue from a combination of product sales, license fees and milestone payments in connection with strategic partnerships, and royalties from the sale of products developed under licenses of our intellectual property. Our ability to generate revenue and become profitable depends primarily on our ability to successfully develop and commercialize or partner our INOpulse and/or BCM product candidates, each of which is currently in clinical development, as well as any product candidates we may advance in the future. We expect that any revenue we may generate will fluctuate from quarter to quarter as a result of the timing and amount of any payments we may receive under future partnerships, if any, and from sales of any products we successfully develop and commercialize. If we fail to complete the development of any of our product candidates currently in clinical development or any future product candidates in a timely manner, or to obtain regulatory approval for such product candidates, our ability to generate future revenue, and our business, results of operations, financial condition and cash flows and future prospects would be materially adversely affected.

Research and Development Expenses

Research and development expenses consist of costs incurred in connection with the discovery and development of our product candidates, including upfront and development milestone payments, related to in-licensed product candidates and technologies.

In order to fairly present our historical information for periods prior to the Spin-Out, certain departmental expenses from Ikaria have been allocated to us. The allocations were applied to us for the purpose of presenting our company as a stand-alone entity. Direct and indirect costs for periods prior to the Spin-Out related to the INOpulse and BCM clinical programs have been allocated to us. All allocations were based on actual costs

incurred. For purposes of allocating non-project specific expenses, each Ikaria department head provided information as to the percentage of employee time incurred on our behalf.

Research and development expenses primarily consist of:

- employee-related expenses, including salary, benefits and stock-based compensation expense;
- expenses incurred under agreements with contract research organizations, investigative sites that conduct our clinical trials and consultants that conduct a portion of our pre-clinical studies;
- expenses relating to vendors in connection with research and development activities;
- the cost of acquiring and manufacturing clinical trial materials;
- facilities, depreciation of fixed assets and allocated expenses;
- lab supplies, reagents, active pharmaceutical ingredients and other direct and indirect costs in support of our pre-clinical and clinical activities;
- device development and drug manufacturing engineering;
- license fees related to in-licensed products and technology; and
- costs associated with non-clinical activities and regulatory approvals.

We expense research and development costs as incurred.

Conducting a significant amount of research and development is central to our business model. Product candidates in late stages of clinical development generally have higher development costs than those in earlier stages of clinical development primarily due to the increased size and duration of late-stage clinical trials. We plan to increase our research and development expenses for the foreseeable future as we seek to continue multiple clinical trials for our INOpulse and BCM programs, including to potentially advance INOpulse for PH-IPF, and seek to identify additional early-stage product candidates.

We track external research and development expenses and personnel expenses on a program-by-program basis. We use our employee and infrastructure resources, including regulatory affairs, quality, biometrics support and program management, across our two clinical development programs and have included these expenses in research and development infrastructure. Research and development laboratory and depreciation expenses are also not allocated to a specific program and are included in research and development infrastructure. Engineering activities related to INOpulse and the manufacture of cylinders related to INOpulse are included in INOpulse engineering.

INOpulse for PAH

We completed a randomized, placebo-controlled, double-blind Phase 2 clinical trial of INOpulse for PAH in October 2014. The goal of the trial is to determine the safety, tolerability and efficacy of two different doses of INOpulse for PAH. We believe the results of this trial provide sufficient indication of clinical benefit and safety to continue development of INOpulse for PAH in pivotal Phase 3 clinical trials. We had an End of Phase 2 meeting with the FDA on January 8, 2015. Based on feedback from the FDA at this meeting, we are moving forward with Phase 3 development and plan to conduct two adequate and well-controlled confirmatory Phase 3 clinical trials, either sequentially or in parallel. In March 2015, we requested feedback on the proposed trial design from the Scientific Advice Working Party of the EMA. We intend to finalize the clinical trial design following additional discussions with the FDA as well as with other regulatory authorities, including with the EMA.

INOpulse for PH-COPD

We completed a randomized, placebo-controlled, double-blind, dose-confirmation Phase 2 clinical trial of INOpulse for PH-COPD in July 2014. We have received results from this trial, and we are currently evaluating our trial design for a Phase 2b clinical trial and plan to finalize our protocol following discussions with regulatory authorities in the United States and the European Union.

BCM

We initiated a clinical trial of BCM, which we refer to as our PRESERVATION I trial, in December 2011 and enrolled the first patient in April 2012. This trial is a CE mark registration trial in the European Union and, if the results are positive, we intend to conduct a pivotal trial designed to support registration in the United States. We completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure at almost 90 clinical sites in Europe, Australia, North America and Israel. We expect to report top line results in mid-2015.

Research and Development Infrastructure

We invest in regulatory, quality, pharmacovigilance and program management activities, which are expensed as incurred. These activities primarily support our INOpulse and BCM clinical development programs.

INOpulse Engineering

We have invested a significant amount of funds in INOpulse, which is configured to be highly portable and compatible with available modes of long-term oxygen therapy via nasal cannula delivery. Our Phase 2 clinical trials of INOpulse for PAH and INOpulse for PH-COPD utilized the first generation INOpulse DS device. We are near completion of a second generation INOpulse Mark2 device, which we refer to as the Mark2, as well as a custom triple-lumen cannula, each of which we believe will significantly improve several characteristics of our INOpulse delivery system but will require prototype manufacturing and bench top testing, as well as verification and validation. We have also invested in design and engineering technology, through Ikaria, for the manufacture of our drug cartridges. We currently rely on Ikaria for manufacturing of our INOpulse drug cartridges. In addition, Ikaria is conducting substantial engineering and stability testing work with respect to the INOpulse devices on our behalf pursuant to the TSA. In February 2015, we entered into an agreement with Flextronics to manufacture and service the Mark2 devices that we expect to use in future clinical trials of INOpulse for PAH and INOpulse for PH-COPD.

It is difficult to determine with certainty the duration and completion costs of our current or any future pre-clinical programs and any of our current or future clinical trials for our INOpulse and BCM programs and any future product candidates we may advance, or if, when or to what extent we will generate revenue from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors, including the uncertainties of any future clinical trials and pre-clinical studies, uncertainties in clinical trial enrollment rate and significant and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability. A change in the outcome of any of these variables with respect to the development of a product candidate could change significantly the costs and timing associated with the development of that product candidate. For example, if the FDA or other regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time with respect to the development of that product candidate. We will determine which programs to pursue and how much to fund each program in

response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential, including the likelihood of regulatory approval on a timely basis.

General and Administrative Expenses

General and administrative expenses consist principally of salaries and costs related to executive, finance, business development, marketing, legal and human resources functions, either through direct expenses or the TSA. Other general and administrative expenses include patent filing, patent prosecution, professional fees for legal, insurance, consulting, information technology and auditing and tax services not otherwise included in research and development expenses.

We believe that the following factors, among others, will affect the amount of our general and administrative expenses in the future:

- we expect to incur additional general and administrative expenses to support ourselves as a stand-alone company, such as investing in new telecommunications services;
- we expect to incur, prior to the termination of the TSA and the 2015 Services Agreement, expenses in preparation for replacing services that are currently provided by Ikaria pursuant to the TSA and the 2015 Services Agreement, which will likely include dedicated accounting and human resources functions and certain information technology services;
- we expect to incur reduced general and administrative expenses payable to Ikaria upon the expiration of the TSA and the 2015 Services Agreement, in each case in February 2016;
- we expect to incur increased general and administrative expenses to support our research and development activities, which we expect will expand as we continue to pursue the development of our product candidates;
- we expect our general and administrative expenses will increase as a result of increased payroll, expanded infrastructure, higher consulting, legal, accounting and investor relations costs, director compensation and director and officer insurance premiums associated with being a public company; and
- we may begin to incur expenses related to sales and marketing of our product candidates in anticipation of commercial launch before we receive regulatory approval of a product candidate.

Results of Operations

Comparison of Years Ended December 31, 2014 and 2013

The following table summarizes our results of operations for the years ended December 31, 2014 and 2013, together with the changes in these items in dollars and as a percentage.

	Year Ended December 31,			
(Dollar amounts in thousands)	**2014**	**2013**	**$ Change**	**% Change**
Research and development expenses:				
BCM	$ 13,660	$ 17,266	$ (3,606)	(21)%
PAH	11,319	8,099	3,220	40%
PH-COPD	3,026	8,420	(5,394)	(64)%
Clinical programs	28,005	33,785	(5,780)	(17)%
Research and development infrastructure	11,675	14,000	(2,325)	(17)%
INOpulse engineering	6,298	5,200	1,098	21%
Total research and development expenses	45,978	52,985	(7,007)	(13)%
General and administrative	13,775	9,013	4,762	53%
Total operating expenses	59,753	61,998	(2,245)	(4)%
Interest income	(79)	—	(79)	N/A
Net loss and comprehensive loss	$ (59,674)	$ (61,998)	$ 2,324	(4)%

Total Operating Expenses. Total operating expenses for the year ended December 31, 2014 were $59.8 million compared to $62.0 million for the year ended December 31, 2013, a decrease of $2.2 million, or 4%. This decrease was primarily due to reductions in research and development expenses pertaining to our BCM and INOpulse for PH-COPD programs and to research and development infrastructure expenses, partially offset by increases in general and administrative expenses, research and development expenses pertaining to INOpulse for PAH and INOpulse engineering expenses.

Research and Development Expenses. Total research and development expenses for the year ended December 31, 2014 were $46.0 million compared to $53.0 million for the year ended December 31, 2013, a decrease of $7.0 million, or 13%. Total research and development expenses consisted of the following:

- BCM research and development expenses for the year ended December 31, 2014 were $13.7 million compared to $17.3 million for the year ended December 31, 2013, a decrease of $3.6 million, or 21%. The decrease primarily resulted from the effect of certain non-recurring manufacturing costs in the 2013 period, as well as a decrease in the pre-clinical activities that we conducted with respect to BCM during the year ended December 31, 2014. This decrease was partially offset by an increase in clinical trial costs as a result of an increase in patient enrollments in the year ended December 31, 2014 as compared to the prior year period.

- PAH research and development expenses for the year ended December 31, 2014 were $11.3 million compared to $8.1 million for the year ended December 31, 2013, an increase of $3.2 million, or 40%. The increase was primarily due to higher clinical trial expenses in the year ended December 31, 2014, driven by higher patient enrollment costs as compared to the prior year period, as well as increased spending in respect of development of the Mark2 in preparation for our anticipated Phase 3 clinical trial.

- PH-COPD research and development expenses for the year ended December 31, 2014 were $3.0 million compared to $8.4 million for the year ended December 31, 2013, a decrease of $5.4 million, or 64%. The decrease primarily resulted from lower dosing trial costs as a result of the completion of our Phase 2 clinical trial.

- Research and development infrastructure expenses for the year ended December 31, 2014 were $11.7 million compared to $14.0 million for the year ended December 31, 2013, a decrease of $2.3 million, or 17%. The decrease was primarily the result of reductions in headcount in connection with managing staffing needs to support our INOpulse and BCM clinical programs.

- INOpulse engineering expenses for the year ended December 31, 2014 were $6.3 million compared to $5.2 million for the year ended December 31, 2013, an increase of $1.1 million, or 21%. The increase was primarily due to increases in development costs as we transitioned from the INOpulse DS device to the Mark2.

General and Administrative Expenses. General and administrative expenses for the year ended December 31, 2014 were $13.8 million compared to $9.0 million for the year ended December 31, 2013, an increase of $4.8 million, or 53%. The increase was primarily due to the incremental costs of operating as a stand-alone entity, including professional service fees, executive search costs, the payment of certain retention bonuses and information technology expenditures.

Comparison of Years Ended December 31, 2013 and 2012

The following table summarizes our results of operations for the years ended December 31, 2013 and 2012, together with the changes in these items in dollars and as a percentage.

	Year Ended December 31,			
(Dollar amounts in thousands)	**2013**	**2012**	**$ Change**	**% Change**
Research and development expenses:				
BCM	$ 17,266	$ 14,609	$ 2,657	18%
PAH	8,099	8,544	(445)	(5)
PH-COPD	8,420	1,767	6,653	377
Clinical programs	33,785	24,920	8,865	36
Research and development infrastructure	14,000	10,387	3,613	35
INOpulse engineering	5,200	3,420	1,780	52
Total research and development expenses	52,985	38,727	14,258	37
General and administrative	9,013	7,185	1,828	25
Other operating expenses	—	315	(315)	(100)
Total operating expenses	61,998	46,227	15,771	34
Net loss and comprehensive loss	$ (61,998)	$ (46,227)	$ (15,771)	34%

Total Operating Expenses. Total operating expenses for the year ended December 31, 2013 were $62.0 million compared to $46.2 million for the year ended December 31, 2012, an increase of $15.8 million, or 34%. This increase was primarily due to an increase in research and development expenses pertaining to our BCM and INOpulse for PH-COPD clinical programs, research and development infrastructure, INOpulse engineering and manufacturing, and general and administrative expenses.

Research and Development Expenses. Total research and development expenses for the year ended December 31, 2013 were $53.0 million compared to $38.7 million for the year ended December 31, 2012, an increase of $14.3 million, or 37%. Total research and development expenses consisted of the following:

- BCM research and development expenses for the year ended December 31, 2013 were $17.3 million compared to $14.6 million for the year ended December 31, 2012, an increase of $2.7 million, or 18%. The increase was primarily due to increased enrollment in our PRESERVATION I trial to 120 patients in 2013 from 19 patients in 2012.

- PAH research and development expenses for the year ended December 31, 2013 were $8.1 million compared to $8.5 million for the year ended December 31, 2012, a decrease of $0.4 million, or 5%. The decrease was primarily due to a smaller number of devices being manufactured for our INOpulse for PAH trial in 2013 as compared to 2012, partially offset by increased patient enrollment in the Phase 2 clinical trial of INOpulse for PAH to 47 patients in 2013 from ten patients in 2012.

- PH-COPD research and development expenses for the year ended December 31, 2013 were $8.4 million compared to $1.8 million for the year ended December 31, 2012, an increase of $6.7 million, or 377%. The increase resulted from commencement of the first part of the Phase 2 clinical trial of INOpulse for PH-COPD in 2013.

- Research and development infrastructure expenses for the year ended December 31, 2013 were $14.0 million compared to $10.4 million for the year ended December 31, 2012, an increase of $3.6 million, or 35%. The increase was primarily due to a higher level of professional and consulting fees to support our INOpulse and BCM clinical programs, including those related to program risk analysis, regulatory, biometrics and drug and device safety in 2013.

- INOpulse engineering expenses for the year ended December 31, 2013 were $5.2 million compared to $3.4 million for the year ended December 31, 2012, an increase of $1.8 million, or 52%. The increase was primarily due to increased engineering activity related to the INOpulse devices in 2013.

General and Administrative Expenses. General and administrative expenses for the year ended December 31, 2013 were $9.0 million compared to $7.2 million for the year ended December 31, 2012, an increase of $1.8 million, or 25%. The increase was primarily due to allocated finance costs.

Other Operating Expenses. In 2012, we incurred a $0.3 million restructuring charge recorded for the impairment of fixed assets related to the closure of the research and development facility in Seattle, Washington, as we moved research and development operations to our facilities in North Brunswick, New Jersey.

Liquidity and Capital Resources

Since our inception, we have incurred net losses and negative cash flows from our operations. We incurred net losses of $59.7 million and $62.0 million for the years ended December 31, 2014 and 2013, respectively. Our operating activities used $70.6 million and $57.2 million of cash during the years ended December 31, 2014 and 2013, respectively. As of December 31, 2014, all of the cash used in our operating activities was contributed to us by our former parent company, Ikaria. In addition, we had $17.2 million of working capital and $27.6 million of cash and cash equivalents and restricted cash as of December 31, 2014. We subsequently raised net proceeds of $52.6 million, after deducting underwriting discounts and commissions of $4.2 million and offering costs of $3.2 million, from the sale of common stock in our initial public offering in the first quarter of 2015.

Cash Flows

The following table summarizes our cash flows for the years ended December 31, 2014, 2013 and 2012:

(Dollar amounts in thousands)	Year Ended December 31, 2014	2013	2012
Operating activities	$ (70,562)	$ (57,231)	$ (36,224)
Investing activities	—	(727)	(3,478)
Financing activities	87,377	57,958	39,702
Increase in cash and cash equivalents	$ 16,815	$ —	$ —

Net Cash Used in Operating Activities

Cash used in operating activities for the year ended December 31, 2014 was $70.6 million compared to $57.2 million for the year ended December 31, 2013, an increase of $13.4 million, or 23%. The increase in cash used in operating activities was primarily due to the deposit of escrowed cash in connection with the TSA.

Cash used in operating activities for the year ended December 31, 2013 was $57.2 million compared to $36.2 million for the year ended December 31, 2012, an increase of $21.0 million, or 58%. The increase was primarily driven by clinical development expenses attributable to activity in the INOpulse and BCM clinical programs.

Net Cash Used in Investing Activities

Cash used in investing activities for the year ended December 31, 2014 was $0 compared to $0.7 million of cash used in investing activities for the year ended December 31, 2013. The decrease in cash used in investing activities was primarily the result of a reduction in capital expenditures due to the timing of device investments to support our clinical trials.

Cash used in investing activities for the year ended December 31, 2013 was $0.7 million compared to $3.5 million for the year ended December 31, 2012, a decrease of $2.8 million, or 79%. The decrease was primarily the result of a reduction in capital expenditures due to the timing of device investments to support our clinical trials.

Net Cash Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2014 was $87.4 million compared to $58.0 million for the year ended December 31, 2013, an increase of $29.4 million, or 51%. The increase was primarily due to a cash contribution of $80.0 million from Ikaria in connection with the Spin-Out.

Cash provided by financing activities for the year ended December 31, 2013 was $58.0 million compared to $39.7 million for the year ended December 31, 2012, an increase of $18.3 million, or 46%. The increase was due to the increased net investment by Ikaria in 2013.

Plan of Operations and Future Funding Requirements

Our primary uses of capital are, and we expect will continue to be, compensation and related expenses, third-party clinical research and development services, contract manufacturing services, laboratory and related supplies, clinical costs, legal and other regulatory expenses and general overhead costs.

We believe our existing cash and cash equivalents and restricted cash as of December 31, 2014, together with the proceeds of our initial public offering completed in February 2015, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements at least into mid-2016. We have based these estimates on assumptions that may prove to be wrong, and we may exhaust our capital resources sooner than we expect. In addition, the process of testing product candidates in clinical trials is costly, and the timing of progress in clinical trials is uncertain. Because our product candidates are in clinical development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts that will be necessary to successfully complete the development and commercialization of our product candidates or whether, or when, we may achieve profitability. Our future capital requirements will depend on many factors, including:

- the timing, progress and results of our ongoing and planned clinical trials of INOpulse for PAH, INOpulse for PH-COPD and BCM;
- our ability to manufacture sufficient supply of our product candidates and the costs thereof;
- discussions with regulatory agencies regarding the design and conduct of our clinical trials and the costs, timing and outcome of regulatory review of our product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution for any of our product candidates for which we receive marketing approval;
- the number and development requirements of any other product candidates we pursue;
- our ability to enter into collaborative agreements and achieve milestones under those agreements;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;

- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- our expenses as a stand-alone company; and
- the extent to which we acquire or in-license other products and technologies.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity and debt offerings, existing working capital and funding from potential future collaboration arrangements. To the extent that we raise additional capital through the future sale of equity or debt, the ownership interest of our existing stockholders will be diluted, and the terms of such securities may include liquidation or other preferences that adversely affect the rights of our existing stockholders. If we raise additional funds through strategic partnerships in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following is a summary of our long-term contractual cash obligations as of December 31, 2014 (in thousands):

	Payments Due by Period ($)				
Contractual Obligations	**Total**	**Less than 1 year**	**1 to 3 years**	**3 to 5 years**	**More than 5 years**
Operating Lease Obligations(1)	23	23	—	—	—
Transition Services Agreement(2)	10,812	9,264	1,548	—	—

(1) Operating lease obligations reflect our obligation to make payments in connection with a lease for our operating facilities. The amounts in the table do not include our rent obligation of $115,000 from March 15, 2015 through March 15, 2016 under an extension to our lease that we signed subsequent to December 31, 2014.

(2) Under the TSA, Ikaria provides certain administrative and other services to us for a period of 24 months following February 9, 2014, unless terminated earlier. Ikaria also provides us with the use of office space and research laboratory facilities at Ikaria's headquarters located in Hampton, New Jersey. In exchange for the services provided by Ikaria pursuant to the TSA, we pay to Ikaria a service fee in the amount of $772,000 per month and reimburse Ikaria for any out of pocket expenses, any taxes imposed on Ikaria in connection with the provision of services under the TSA and Ikaria's costs and expenses incurred in connection with the performance of any extraordinary services. The monthly service fee is payable by us regardless of the frequency or quantity of services actually utilized by us, and our obligation to pay such monthly service fee for 24 months will survive any early termination of the TSA. At the time of the Spin Out, we deposited the sum of $18.5 million, representing the aggregate of the $772,000 monthly service fees payable by us under the TSA, in escrow to guarantee payment of the monthly service fees.

Under the 2015 Services Agreement, which became effective on January 1, 2015 and expires in February 2016, Ikaria provides to us certain information technology and device servicing services. In exchange for the services provided by Ikaria pursuant to the 2015 Services Agreement, we will pay to Ikaria fees that total, in the aggregate, approximately $215,000, subject to the termination of the 2015 Services Agreement.

Milestone and royalty payments associated with our license agreement with BioLine have not been included in the above table of contractual obligations as we cannot reasonably estimate if or when they will occur. Under the terms of the license agreement, if we achieve certain clinical and regulatory events specified in

the license agreement, we will be obligated to pay milestone payments to BioLine, which could total, in the aggregate, up to $115.5 million, and if we achieve certain commercialization targets specified in the license agreement, we will be obligated to pay additional milestone payments to BioLine, which could total, in the aggregate, up to $150.0 million. In addition, we will be obligated to pay BioLine a specified percentage of any upfront consideration we receive for sublicensing BCM, as well as royalties on net sales, if any, at a percentage ranging from 11% to 15%, depending on net sales level, of any approved product containing BCM, subject to offsets for specified payments to third parties made in connection with BCM. Further, we have agreed to reimburse BioLine for certain legal fees in the amount of $250,000 following completion of our initial public offering.

In the course of our normal business operations, we also enter into agreements with contract service providers and others to assist in the performance of our research and development and manufacturing activities. We can elect to discontinue the work under these contracts and purchase orders at any time with notice, and such contracts and purchase orders do not contain minimum purchase obligations.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable Securities and Exchange Commission rules.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to research and development expense, impairment of long-lived assets, stock-based compensation and income taxes. We base our estimates on historical experience, known trends and events and various other factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in Note 2 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Research and Development Expense

Research and development costs are expensed as incurred. These expenses include the costs of our proprietary research and development efforts, as well as costs incurred in connection with certain licensing arrangements. Upfront and milestone payments made to third parties in connection with research and development collaborations are expensed as incurred up to the point of regulatory approval. Payments made to third parties upon or subsequent to regulatory approval are capitalized and amortized over the remaining useful life of the related product. We also expense the cost of purchased technology and equipment in the period of purchase if we believe that the technology or equipment has not demonstrated technological feasibility and does not have an alternative future use. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and are recognized as research and development expense as the related goods are delivered or the related services are performed.

As part of the process of preparing our financial statements, we are required to estimate our accrued research expenses. This process involves reviewing open contracts and purchase orders, communicating with applicable personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. The majority of our service providers invoice us monthly in arrears for services performed. We make estimates of our accrued research and development expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include:

- fees paid to contract research organizations in connection with clinical trials;
- fees paid to investigative sites in connection with clinical trials;
- fees paid to contract manufacturers in connection with the production of clinical trial materials; and
- fees paid to vendors in connection with the pre-clinical development activities.

We base our expenses related to research and development and clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple third parties, including research institutions and contract research organizations that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing the research and development service fees, we consider the terms of each agreement, the time period over which the services will be performed and the level of effort required to complete the service. If the actual timing of the performance of the services or the level of effort varies from our estimate, we adjust the accrual accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period. Based on our level of accrued research and development expenses as of December 31, 2014, if our estimates are too high or too low by 5%, this may result in an adjustment to our accrued research and development expenses in future periods of approximately $0.3 million.

Impairment of Long-Lived Assets

Long-lived assets, such as property, plant and equipment, are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to estimated undiscounted expected future cash flows. If the carrying amount of an asset exceeds its estimated future cash flows, an impairment charge is recognized for the amount by which the carrying amount of the asset exceeds the fair value of the asset. Assets to be sold are no longer depreciated and are reclassified outside of property, plant and equipment at the lower of the carrying amount or fair value less costs to sell.

Stock-Based Compensation

We issue, and prior to the Spin-Out Ikaria, our former parent, issued, stock-based awards to employees and non-employees in the form of stock options and RSUs. The stock-based compensation expense recorded for the periods prior to the Spin-Out presented in our audited financial statements, included elsewhere in this Annual Report on Form 10-K, represents an allocation of Ikaria's stock-based compensation expense for employees and non-employees whose time was attributed to our business prior to the Spin-Out and, as a result, has been allocated to us for accounting purposes.

Ikaria applied, and we apply, the fair value recognition provisions of the Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 718, Compensation-Stock Compensation, or ASC 718. ASC 718 requires all stock-based payments to employees, including grants of employee stock options and RSUs and modifications to existing stock options and RSUs, to be recognized in the statements of operations based on their fair values. Ikaria recognized, and we recognize, the compensation expense of stock-based awards on a straight-line basis over the vesting period of the award for employees and non-employees or sooner if the award is immediately vested. Compensation expense related to stock-based awards is subject to a number of estimates, including the estimated volatility and underlying fair value of our common stock, as well as the estimated life of the awards.

Ikaria estimated, and we estimate, the fair value of stock-based awards to employees and non-employees using the Black-Scholes-Merton option-pricing model, which requires the input of highly subjective assumptions, including (a) the fair value of the underlying stock, (b) the expected volatility of the underlying stock, (c) the expected term of the award, (d) the risk-free interest rate and (e) expected dividends. Due to the lack of a public market for the trading of Ikaria common stock and our equity securities and a lack of company-specific historical and implied volatility data for either company, we and Ikaria based our respective estimates of expected volatility on the historical volatility of a group of similar companies that are publicly traded. For the volatility analyses, we and Ikaria selected companies with comparable characteristics to our respective companies, including enterprise value, risk profile and position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. We and Ikaria computed the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of our respective stock-based awards. We will apply this process for purposes of our future stock-based compensation expense until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. Because we and Ikaria had minimal historical information to develop expectations about future exercise patterns for our respective stock option grants, in each case, the expected term is based on an average of the expected term of options granted by our respective publicly traded industry peers. The risk-free interest rates for periods within the expected life of the awards are based on the U.S. Treasury yield curve in effect during the period in which the awards were granted.

In addition, Ikaria was, and we are, required to estimate forfeitures at the time of grant, and revise those estimates in subsequent periods if actual forfeitures differ from estimates. Ikaria used, and we use, historical data to estimate pre-vesting forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

For the periods presented prior to the Spin-Out, the weighted average grant date fair value of stock options granted to employees and directors of Ikaria and the weighted average assumptions used by Ikaria to estimate the grant date fair value of the options using the Black-Scholes-Merton option pricing model were:

	2013	2012
Weighted average grant date fair value	$ 1.95	$ 2.40
Valuation assumptions:		
Risk-free interest rate	0.90%	0.83%
Expected volatility	46.5%	47.6%
Expected term (in years)	5.00	5.00
Expected dividend yield	—	—

There were no Ikaria options issued during the period from January 1, 2014 through February 11, 2014.

Ikaria has historically granted its stock options at exercise prices not less than the fair value of its common stock. Ikaria was a private company with no active public market for its common stock. Therefore, its board of directors periodically determined for financial reporting purposes the estimated fair value of its common stock using valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately Held Company Equity Securities Issued as Compensation*, also known as the Practice Aid.

The compensation expense for the RSUs was based on the grant date fair value of the RSU, which was based on the fair value of the underlying stock.

Prior to the Spin-Out, Ikaria adjusted its outstanding stock options to reflect the Spin-Out. In connection with such adjustment, we issued to certain employees and directors of ours or of Ikaria, as well as certain accredited investors, options to purchase an aggregate of 618,212 of our non-voting membership units, at a weighted average exercise price of $7.24 per unit, which we refer to as the Bellerophon Options. The exercise price of each Bellerophon Option was determined by allocating the exercise price of each outstanding Ikaria stock option held by such individuals to Ikaria and us using a ratio of 85% and 15%, respectively, which reflected the relative value of each entity at the time of the Spin-Out. Each Bellerophon Option has the same expiration date as the corresponding Ikaria stock option. Prior to and in connection with the Spin-Out, we issued to certain employees and directors of ours or of Ikaria and certain accredited investors RSUs in respect of an aggregate of 372,947 of our non-voting membership units, which we refer to as the Bellerophon RSUs. In connection with the Spin-Out, the vesting of each Bellerophon Option and each Bellerophon RSU was fully accelerated.

Our stock-based compensation expense for periods prior to the Spin-Out represents our allocable portion of Ikaria's stock-based compensation expense for the applicable periods based on the allocation percentages of our cost centers, which were determined based on specific identification or the proportionate percentage of employee time or headcount to the respective total Ikaria employee time or headcount. Our allocable portion of Ikaria's stock-based compensation expense for the years ended December 31, 2014, 2013 and 2012 was approximately $0.3 million, $1.7 million and $1.5 million, respectively. Because certain of these amounts relate to Ikaria stock-based awards, the amounts presented are not necessarily indicative of our future performance and do not necessarily reflect the stock-based compensation or compensation expense that we would have experienced as a stand-alone company for these periods.

In October 2011, Ikaria approved a special dividend plan, which provided for dividend equivalent rights for options, RSUs and other equity awards granted under its equity award plans. Pursuant to the special dividend plan, in the event that Ikaria's board of directors declared a dividend, each employee of Ikaria who held equity awards was eligible to receive a cash payment equal to the amount of the dividend per share, multiplied by the number of equity awards outstanding. The payment was payable as of the declaration date for vested options. For unvested options and unvested RSUs, payment was due upon vesting. As of December 31, 2013, the allocated portion of the special dividend bonus payable was $6.1 million, of which $1.8 million was reflected in other current liabilities and $4.3 million was reflected in non-current liabilities. The full amount of our allocated portion of the special dividend bonus payable was fully paid on our behalf by Ikaria prior to the Spin-Out.

On June 20, 2014, following the Spin-Out, we granted options to purchase 514,266 of our non-voting units with an exercise price of $13.28 per non-voting unit. As we were a private company with no active public market for our equity securities at the time, the estimated fair value of one of our non-voting units as of June 20, 2014 was determined by our board of directors to be $13.28. In making this determination, our board of directors used a contemporaneous valuation based on the income approach, performed in accordance with the guidance enumerated in the Practice Aid. For the income approach, we used the discounted cash flow method to estimate the present value of the future monetary benefits expected to flow to the owners of the business. The contemporaneous valuation also considered factors enumerated in Revenue Ruling 59-60, which serves as a

general guideline for the valuation of closely held securities. In addition, we considered all objective and subjective factors that we believe to be relevant to such valuation, including our best estimate of our business condition, prospects and operating performance at the valuation date. Within the contemporaneous valuation performed, a range of factors and assumptions were used. The significant factors, many of them complex and highly subjective, included:

- estimates of our future cash flows and the appropriate discount rate;
- the nature and history of our business enterprise;
- the assessment of key value drivers for our business enterprise;
- the economic outlook in general and the condition and outlook of our industry in particular;
- the financial condition of our business and the book value of our equity interests;
- the likelihood of our achieving a liquidity event; and
- prior sales of equity interests of companies engaged in the same or similar lines of business that have their stocks actively traded in a free and open market.

The following are the assumptions used in estimating the fair value of options issued during the year ended December 31, 2014.

	Year Ended December 31, 2014
Valuation assumptions:	
Risk-free interest rate	1.71%
Expected volatility	90.00%
Expected term (in years)	6.1
Expected dividend yield	0.00%

Since our initial public offering, the exercise price per share of all option grants has been set at the closing price of our common stock on the NASDAQ Global Market on the applicable date of grant.

For the years ended December 31, 2014, 2013 and 2012, we recorded stock-based expenses as follows:

	Year Ended December 31,		
(in thousands)	2014	2013	2012
Research and development	$ 271	$ 1,120	$ 882
General and administrative	1,568	601	567
Total expense	$ 1,839	$ 1,721	$ 1,449

Income Taxes

During the periods presented prior to the Spin-Out, we did not file separate tax returns, as we were included in the tax groupings of other Ikaria entities within the respective entity's tax jurisdiction. As such, the income tax provision included in our financial statements for such periods has been calculated using the separate return method, as if we filed a separate tax return in each of our respective tax jurisdictions.

For financial reporting purposes, we have historically recorded no tax expense or benefit due to our operating loss position. A valuation allowance was established on net deferred tax assets as of periods prior to the Spin-Out because management believed that it was more likely than not that our net deferred tax assets will not be realized.

For periods prior to the Spin-Out, deferred tax assets and liabilities were recognized for the estimated future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities were measured using enacted tax rates in effect for the year in which those temporary differences are expected to be recovered or settled. When we became a stand-alone company at the date of the Spin-Out, deferred taxes are no longer recorded. We have elected to be treated as a partnership for tax purposes. Although we were a limited liability company until we converted into a corporation in February 2015, one of our subsidiaries is a C-corporation and is subject to state and federal income taxes. This subsidiary had an immaterial loss in 2014 and its deferred taxes are fully reserved.

For periods prior to the Spin-Out, we recognized the benefit of an uncertain tax position that we have taken on income tax returns prepared under a separate return method if such tax position is more likely than not to be sustained on examination by the taxing authorities, based on the technical merits of the position. These tax benefits are measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate resolution. Unrecognized tax benefits related to net operating loss carryforwards or tax credit carryforwards are presented as a reduction to the related gross deferred tax asset. Unrecognized tax benefits for which a net operating loss carryforward or tax credit carryforward is not available are presented as a liability. A liability for unrecognized tax benefits is classified as non-current unless the liability is expected to be settled in cash within 12 months of the reporting date.

Certain deferred tax assets and liabilities and uncertain tax positions that arose as a result of Ikaria's past activities, such as federal and state net operating loss carryforwards, research and development credit carryforwards and acquired in-process research and development, were not transferred to us in connection with the Spin-Out and continued to constitute assets and liabilities of Ikaria subsequent to the date of the Spin-Out.

Recently Adopted Accounting Standards

In May 2014, the FASB issued Accounting Standards Update No. 2014-09, or ASU 2014-09, Revenue from Contracts with Customers (Topic 606). ASU 2014-09 supersedes the revenue recognition requirements in Accounting Standards Update No. 2009-13, Revenue Recognition (Topic 605) and requires entities to recognize revenue in a way that depicts the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled to in exchange for those goods or services. ASU 2014-09 is effective for annual reporting periods beginning after December 15, 2016, including interim periods within that reporting period, and is to be applied either retrospectively to each prior reporting period presented or retrospectively with the cumulative effect recognized at the date of initial application. Early application is not permitted. Although we do not generate revenues currently, management is in the process of evaluating the potential impact from the adoption of this guidance.

In June 2014, the FASB issued Accounting Standards Update No. 2014-10, or ASU 2014-10, Development Stage Entities (Topic 915): Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation. ASU 2014-10 eliminates the distinction of a development stage entity as well as certain related disclosure requirements, including the elimination of inception-to-date information on the statements of operations, members' equity and cash flows. For public business entities, the amendments in ASU 2014-10 are effective prospectively for annual reporting periods beginning after December 15, 2014, and interim periods within those annual periods, and for other entities, the amendments are effective for annual reporting periods beginning after December 15, 2014, and interim reporting periods beginning after December 15, 2015. Early application is permitted. We have adopted ASU 2014-10 for the year ended December 31, 2014.

In June 2014, the FASB issued Accounting Standards Update No. 2014-12, or ASU 2014-12, Compensation—Stock Compensation (Topic 718): Accounting for Share-Based Payments When the Terms of an Award Provide That a Performance Target Could Be Achieved after the Requisite Service Period. ASU 2014- 12 clarifies the proper method of accounting for share-based payments when the terms of an award provide that a performance target could be achieved after the requisite service period. ASU 2014-12 requires that a performance target that affects vesting and that could be achieved after the requisite service period be treated as a performance condition. The performance target should not be reflected in estimating the grant-date fair value of the award. Compensation cost should be recognized in the period in which it becomes probable that the performance target will be achieved and should represent the compensation cost attributable to the period(s) for which the requisite service has already been rendered. The amendments in ASU 2014-12 are effective for annual periods and interim periods within those annual periods beginning after December 15, 2015. Earlier adoption is permitted. We will adopt this guidance if and when we issue share-based awards with performance targets.

In August 2014, the FASB issued Accounting Standards Update No. 2014-15, or ASU 2014-15, Presentation of Financial Statements—Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern. ASU 2014-15 should reduce diversity in the timing and content of footnote disclosures. ASU 2014-15 requires management to assess an entity's ability to continue as a going concern by incorporating and expanding upon certain principles that are currently in U.S. auditing standards. Specifically, it (1) provides a definition of the term substantial doubt, (2) requires an evaluation every reporting period including interim periods, (3) provides principles for considering the mitigating effect of management's plans, (4) requires certain disclosures when substantial doubt is alleviated as a result of consideration of management's plans, (5) requires an express statement and other disclosures when substantial doubt is not alleviated, and (6) requires an assessment for a period of one year after the date that the financial statements are issued (or available to be issued). The amendments in ASU 2014-15 are effective for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. Early application is permitted. We are currently evaluating the impact the adoption of ASU 2014-15 will have on our financial statements.

JOBS Act

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. These provisions include:

- reduced disclosure about our executive compensation arrangements;
- exemption from the non-binding advisory votes on executive compensation, including golden parachute arrangements; and
- exemption from the auditor attestation requirement in the assessment of our internal controls over financial reporting.

Generally, we may take advantage of these exemptions for up to five years or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1.0 billion in annual revenue, we have more than $700.0 million in market value of our stock held by non-affiliates or we issue more than $1.0 billion of non-convertible debt over a three-year period. We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of certain reduced reporting burdens in this Annual Report on Form 10-K. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth

company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2014, we had cash and cash equivalents and restricted cash of approximately $27.6 million, consisting primarily of demand deposits with U.S. banking institutions (other than restricted cash, which is held in escrow). Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in cash and cash equivalents. Due to the short-term duration of our deposits and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our deposits.

Item 8. Financial Statements and Supplementary Data

Index to Financial Statements

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders
Bellerophon Therapeutics, Inc.:

We have audited the accompanying consolidated balance sheets of Bellerophon Therapeutics LLC and subsidiaries as of December 31, 2014 and 2013, and the related consolidated statements of operations and comprehensive loss, changes in members' equity and invested equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2014. These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of Bellerophon Therapeutics LLC and subsidiaries as of December 31, 2014 and 2013, and the results of their operations and their cash flows for each of the years in the three-year period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

/s/ KPMG LLP

Short Hills, New Jersey
March 31, 2015

BELLEROPHON THERAPEUTICS LLC

Consolidated Balance Sheets

(Amounts in thousands, except unit amounts)

	December 31, 2014	December 31, 2013
Assets		
Current assets:		
Cash and cash equivalents	$ 16,815	$ —
Restricted cash	9,264	—
Prepaid expenses and other current assets	1,602	1,552
Total current assets	27,681	1,552
Restricted cash, non-current	1,548	—
Deferred transaction costs	2,466	—
Property and equipment, net	1,696	2,084
Total assets	$ 33,391	$ 3,636
Liabilities and members' equity and invested equity (deficit)		
Current liabilities:		
Accounts payable	$ 376	$ 1,368
Accrued research and development	6,666	7,591
Accrued expenses	2,751	3,194
Due to Ikaria, Inc.	661	—
Other current liabilities	—	1,839
Total current liabilities	10,454	13,992
Allocated portion of Ikaria special dividend payable	—	4,273
Other liabilities	—	1,108
Total liabilities	10,454	19,373
Commitments and contingencies (Note 13)		
Members' equity:		
Members' equity, 94,273,819 voting units authorized, 7,524,196 voting units issued and outstanding at December 31, 2014; 19,416,481 non-voting units authorized, 381,129 non-voting units issued and outstanding at December 31, 2014	77,156	—
Accumulated deficit	(54,219)	—
Total members' equity	22,937	—
Invested equity (deficit):		
Investment by Ikaria, Inc.	—	160,778
Accumulated deficit	—	(176,515)
Total invested deficit	—	(15,737)
Total liabilities and members' equity and invested equity (deficit)	$ 33,391	$ 3,636

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS LLC

Consolidated Statements of Operations and Comprehensive Loss

(Amounts in thousands, except unit and per unit amounts)

	Year Ended December 31,		
	2014	2013	2012
Operating expenses:			
Research and development	$ 45,978	$ 52,985	$ 38,727
General and administrative	13,775	9,013	7,185
Other operating expense	—	—	315
Total operating expenses	59,753	61,998	46,227
Interest income	79	—	—
Pre-tax loss	(59,674)	(61,998)	(46,227)
Income tax benefit (expense)	—	—	—
Net loss and comprehensive loss	$ (59,674)	$ (61,998)	$ (46,227)
Net loss per unit:			
Basic and diluted	$ (7.56)		
Weighted average units outstanding:			
Basic and diluted	7,898,289		

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS LLC

Consolidated Statements of Changes in Members' Equity and Invested Equity (Deficit)

(Amounts in thousands)

	Investment by Ikaria, Inc.	Accumulated deficit	Total invested equity (deficit)	Membership units	Members' equity	Total members' equity
Balance December 31, 2011	$ 65,828	$ (68,290)	$ (2,462)			
Net loss	—	(46,227)	(46,227)			
Investment by Ikaria, Inc., net	37,573	—	37,573			
Balance December 31, 2012	$ 103,401	$ (114,517)	$ (11,116)			
Net loss	—	(61,998)	(61,998)			
Investment by Ikaria, Inc., net	57,377	—	57,377			
Balance December 31, 2013	$ 160,778	$ (176,515)	$ (15,737)			
Net loss from January 1, 2014 through February 11, 2014, prior to Spin-Out	—	(5,455)	(5,455)			
Investment by Ikaria, Inc., net prior to Spin-Out	7,547	—	7,547			
Additional investment by Ikaria, Inc. for settlement of liabilities prior to Spin-Out	9,196	—	9,196			
Balance February 11, 2014	$ 177,521	$ (181,970)	$ (4,449)			
Contribution by Ikaria, Inc. of net assets to Bellerophon in connection with Spin-Out	(177,521)	181,970	4,449	7,899,251	$ 75,551	$ 75,551
Net loss from February 12, 2014 through December 31, 2014	—	(54,219)	—		—	(54,219)
Stock-based compensation	—	—	—		1,568	1,568
Exercise of options	—	—	—	8,182	66	66
Repurchase of units	—	—	—	(2,108)	(29)	(29)
Balance December 31, 2014	$ —	$ (54,219)	$ —	7,905,325	$ 77,156	$ 22,937

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS LLC

Consolidated Statements of Cash Flows

(Amounts in thousands)

	Year Ended December,		
	2014	2013	2012
Cash flows from operating activities:			
Net loss	$ (59,674)	$ (61,998)	$ (46,227)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	388	429	85
Stock-based compensation	1,839	1,721	1,449
Other items	—	149	315
Loss on disposal of property, plant and equipment, net	—	—	2,840
Changes in operating assets and liabilities:			
(Increase) decrease in other current assets and other assets	(50)	94	(11)
Increase in restricted cash	(10,812)	—	—
(Decrease) increase in accounts payable, accrued research and development and accrued expenses	(2,914)	1,655	5,346
Increase in amounts due to Ikaria, Inc.	661	—	—
Increase (decrease) in other liabilities	—	719	(21)
Net cash used in operating activities	(70,562)	(57,231)	(36,224)
Cash flows from investing activities:			
Capital expenditures	—	(727)	(3,478)
Net cash used in investing activities	—	(727)	(3,478)
Cash flows from financing activities:			
Cash contribution from Ikaria, Inc. in connection with Spin-Out	80,000	—	—
Cash contributions from Ikaria, Inc., net	9,252	57,958	39,702
Transaction costs paid	(1,912)	—	—
Proceeds received from exercise of options	66	—	—
Repurchase of units	(29)	—	—
Net cash provided by financing activities	87,377	57,958	39,702
Net change in cash and cash equivalents	16,815	—	—
Cash and cash equivalents at beginning of year	—	—	—
Cash and cash equivalents at end of year	$ 16,815	$ —	$ —
Non-cash investing activities:			
Contribution of property, plant and equipment from Ikaria, Inc.	$ —	$ 83	$ —
Non-cash financing activities:			
Investment by Ikaria, Inc., net	$ 7,491	$ (581)	$ (2,129)

The accompanying notes are an integral part of these consolidated financial statements.

BELLEROPHON THERAPEUTICS LLC

Notes to Consolidated Financial Statements

(1) Organization and Nature of the Business

Bellerophon Therapeutics LLC, or the Company, is a clinical-stage therapeutics company focused on developing innovative products at the intersection of drugs and devices that address significant unmet medical needs in the treatment of cardiopulmonary and cardiac diseases. The Company has two programs in advanced clinical development. The first program, INOpulse, is based on the Company's proprietary pulsatile nitric oxide delivery device. The Company is currently developing two product candidates under its INOpulse program: one for the treatment of pulmonary arterial hypertension, or PAH, for which the Company intends to commence Phase 3 clinical trials in the second half of 2015, and the other for the treatment of pulmonary hypertension associated with chronic obstructive pulmonary disease, or PH COPD, which is in Phase 2 development. The Company's second program is bioabsorbable cardiac matrix, or BCM, which is currently in a placebo-controlled clinical trial designed to support CE mark registration in the European Union. The Company completed enrollment of this trial in December 2014, with 303 patients having completed the treatment procedure, and the Company expects to report top line results in mid-2015. Assuming positive results from this trial, the Company intends to conduct a pivotal pre-market approval trial of BCM beginning in the first half of 2016, which will be designed to support registration in the United States. The Company is developing BCM for the prevention of cardiac remodeling, which often leads to congestive heart failure following an ST-segment elevated myocardial infarction, or STEMI.

The Company's business is subject to significant risks and uncertainties, including but not limited to:

- The risk that the Company will not achieve success in its research and development efforts, including clinical trials conducted by it or its potential collaborative partners.
- The expectation that the Company will experience operating losses for the next several years.
- Decisions by regulatory authorities regarding whether and when to approve the Company's regulatory applications as well as their decisions regarding labeling and other matters which could affect the commercial potential of the Company's products or product candidates.
- The risk that the Company will fail to obtain adequate financing to meet its future capital and financing needs.
- The risk that key personnel will leave the Company and/or that the Company will be unable to recruit and retain senior level officers to manage its business.

The Company was formerly the research and development operating segment of Ikaria Inc., or Ikaria. During the third quarter of 2013 in conjunction with Ikaria's financing activities, Ikaria began reporting financial information for two operating segments: its research and development business and its commercial business. During the fourth quarter of 2013, Ikaria completed an internal reorganization of the assets and subsidiaries of its two operating segments. In connection with the internal reorganization, Ikaria formed the Company as a new wholly-owned subsidiary and transferred the research and development-related assets related to INOpulse for PAH and INOpulse for PH-COPD to the Company and/or its subsidiaries.

On December 24, 2013, Ikaria and Madison Dearborn Partners, or MDP, entered into an agreement and plan of merger, under which MDP would acquire a majority ownership position in Ikaria and existing shareholders retained a minority ownership position in Ikaria through certain merger transactions, or the Merger.

On February 12, 2014, prior to the Merger, Ikaria distributed all of the Company's outstanding units to Ikaria's stockholders in a pro rata distribution through a special dividend, which is referred to as the Spin-Out.

In the Spin-Out, each holder of Ikaria common stock received one voting limited liability company interest in the Company for each share of Ikaria common stock held. There were 7,905,325 units outstanding as of December 31, 2014.

On February 12, 2014, through a series of merger subsidiary transactions, MDP acquired a majority ownership of Ikaria and Ikaria's existing shareholders retained a minority ownership position in Ikaria.

In connection with the Spin-Out, $80.0 million of cash was distributed to the Company. At the time of the Spin-Out, $18.5 million of the $80.0 million cash held by the Company was deposited in escrow to guarantee payment of the monthly services fees payable by the Company to Ikaria in exchange for the services to be provided by Ikaria pursuant to the Company's transition services agreement with Ikaria, or the TSA, during the 24 months following the Spin-Out. At December 31, 2014, the escrowed cash balance was $10.8 million and is classified as restricted cash on the consolidated balance sheet at December 31, 2014, with $9.3 million reflected as current and $1.5 million reflected as non-current. See Note 11—*Related-Party Transactions*.

On February 19, 2015, the Company completed the sale of 5,000,000 shares of common stock, or the IPO, at a price to the public of $12.00 per share, resulting in net proceeds to the Company of $52.6 million after deducting underwriting discounts and commissions of $4.2 million and offering costs of $3.2 million. The Company's common stock began trading on the NASDAQ Global Market under the symbol "BLPH" on February 13, 2015.

(2) Summary of Significant Accounting Policies

(a) Basis of Presentation

The financial statements have been prepared in accordance with generally accepted accounting principles in the United States or GAAP. Intercompany transactions have been eliminated. For periods prior to the Spin-Out, the financial statements were carved out of the consolidated financial statements of Ikaria. Although the financial statements prior to the Spin-Out were prepared on a combined carve-out basis, the financial statements for all periods presented have been labeled "consolidated" financial statements for ease of reference since the most recent balance sheet at December 31, 2014 is a consolidated balance sheet. At the date of the Spin-Out, the historical accumulated deficit of approximately $182.0 million based on the carve-out financial statements through February 11, 2014 was eliminated in the transfer of net assets to the Company. The net loss for the period February 12, 2014 through December 31, 2014 of $54.2 million has been reflected as the accumulated deficit on the December 31, 2014 consolidated balance sheet, representing the net loss since the date of the Spin-Out. Net assets contributed to the Company in the Spin-Out were $75.6 million, including cash of $80.0 million. The results of operations and cash flows from February 12, 2014 through December 31, 2014 and the balance sheet as of December 31, 2014 represent actual results and the financial position of the Company on a stand-alone basis.

On February 2, 2015, the Company effected a reverse unit split of its outstanding units at a ratio of one unit for every 12.5257 units previously held. All unit and per unit data included in these consolidated financial statements reflect the reverse unit split.

The preparation of financial statements requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of costs and expenses during the reporting period, including accrued research and development expenses, stock-based compensation, income taxes and valuation of long-lived assets. Actual results could differ from those estimates.

Management believes that the statements of operations for periods prior to the Spin-Out include a reasonable allocation of costs and expenses incurred by Ikaria which benefited the Company. However, such

amounts may not be indicative of the actual level of costs and expenses that would have been incurred by the Company if it had operated as an independent stand-alone company or of the costs and expenses expected to be incurred in the future. As such, the financial information herein may not necessarily reflect the financial position, results of operations and cash flows of the Company expected in the future or what it would have been had it been an independent stand-alone company during the periods presented.

Direct and indirect costs related to the Company for INOpulse for PAH, INOpulse for PH-COPD and BCM clinical programs have been allocated to the Company for periods prior to February 12, 2014. These allocations were based on either a specific identification basis or, when specific identification was not practicable, proportional cost allocation methods, such as time and wage studies, depending on the nature of the expense. All allocations were based on actual costs incurred. For purposes of allocating non-project specific expenses, each departmental head provided information as to the percentage of employee time incurred on behalf of the Company.

Allocations of general and administrative expenses by Ikaria to the Company for periods prior to February 12, 2014 include allocations of corporate management, finance, information technology, legal, human resources and other overhead expenses, based on an approximate pro-rata headcount of employees.

The Company's balance sheet at December 31, 2013 includes assets and liabilities that were specifically identified and those that were allocated by Ikaria to the Company based on an estimate of the benefit derived from the underlying asset or liability. Ikaria has historically used a centralized approach to cash management and financing of its operations. Prior to the date of the Spin-Out, cash funding for the Company from Ikaria had been accounted for as a capital contribution from Ikaria.

(b) Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity date of three months or less to be cash equivalents.

(c) Restricted Cash

Restricted cash represents amounts held on deposit with a bank in relation to the TSA. The funds are held in an account to settle the required payment to Ikaria for services to be provided in connection with the TSA. The required payments to be paid in excess of one year from the balance sheet date are classified as long-term restricted cash. See Note 11—*Related-Party Transactions*.

(d) Property, Plant and Equipment

Property, plant and equipment are recorded at acquisition cost, which for internally developed assets include labor, materials and overhead. Additions and improvements that increase the value or extend the life of an asset are capitalized. Repairs and maintenance costs are expensed as incurred.

Depreciation is computed using the straight-line method over the estimated useful lives described below:

Asset description	Estimated useful life (years)
Machinery, equipment and furniture	3 - 15

(e) Impairment of Long-Lived Assets

Long-lived assets, such as property, plant and equipment, are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable.

Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to estimated undiscounted expected future cash flows. If the carrying amount of an asset exceeds its estimated future cash flows, an impairment charge is recognized for the amount by which the carrying amount of the asset exceeds the fair value of the asset. Assets to be sold are no longer depreciated and are reclassified outside of property, plant and equipment at the lower of the carrying amount or fair value less costs to sell.

(f) Stock-Based Compensation

The Company accounts for its stock-based compensation in accordance with Accounting Standards Codification 718, Compensation—Stock Compensation, which establishes accounting for stock-based awards exchanged for services and requires companies to expense the estimated fair value of these awards over the requisite service period. The Company recognizes stock-based compensation expense in operations based on the fair value of the award on the date of the grant. The resulting compensation expense is recognized on a straight-line basis over the requisite service period, generally four years or sooner if awards are immediately vested. The Company determines the fair value of stock options issued using a Black-Scholes-Merton option pricing model. Certain assumptions used in the model include expected volatility, dividend yield, risk-free interest rate and expected term. See Note 8—*Stock-Based Compensation* for a description of these assumptions.

Prior to the date of the Spin-Out, stock-based compensation expense for the Company represented an allocation of Ikaria's stock-based compensation expense based on the allocation percentages of the Company's cost centers, which were determined based on specific identification or the proportionate percentage of employee time or headcount to the respective total Ikaria employee time or headcount.

(g) Deferred Transaction Costs

Deferred transaction costs are costs related to the Company's initial public offering, which primarily consist of third-party professional legal, accounting and printing fees associated with the Company's registration statement. These initial public offering costs are deferred and charged against the gross proceeds of an offering when the public offering of equity securities is complete as a reduction of additional paid-in capital. Any deferred costs related to an unsuccessful public offering are expensed in the period in which the company elects to abort the public offering. The Company had deferred transaction costs of $2.5 million as of December 31, 2014, of which $1.9 million had been paid as of December 31, 2014.

(h) Income Taxes

On the date of the Spin-Out, the Company became a stand-alone limited liability company taxed as a partnership. Under this structure, the Company is not subject to income tax at the federal level, with the exception of its C-corporation subsidiary (see below), as its members are liable for the taxes on the Company's income or loss. The Company is subject to various taxes imposed within the states where it operates, however, currently those states do not have a partnership tax. Although the Company was a limited liability company until it converted into a corporation in February 2015, one of its subsidiaries is a C-corporation that is subject to federal and state income taxes. The Company recorded no income tax provision or benefit for the period from February 12, 2014, the date of the Spin-Out, to December 31, 2014 as a result of the net operating losses. The Company did not receive any deferred tax assets or liabilities as a result of the Spin-Out. Net operating losses are transferred to members as they are incurred.

Prior to the date of Spin-Out, the Company did not file a separate tax return as the Company was included in the tax groupings of other Ikaria entities within the respective entity's tax jurisdiction. As such, the income tax provisions for 2013 and 2012 were calculated using the separate return method, as if the Company filed a separate tax return in each of its respective tax jurisdictions. The income tax provisions for 2013 and 2012 included in these carve-out financial statements reflects Ikaria's status as a C-corporation. Subsequent to the date of the Spin-Out, and prior to the conversion of the Company from a limited liability company to a corporation, the Company is taxed as a partnership and does not record deferred tax assets or liabilities.

For financial reporting purposes prior to the Spin-Out, the Company historically recorded no tax expense or benefit due to its operating loss position. A valuation allowance had been established on net deferred tax assets for periods prior to the Spin-Out because management believed that it is more likely than not that the Company's net deferred tax assets will not be realized.

For periods prior to the Spin-Out, deferred tax assets and liabilities were recognized for the estimated future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities were measured using enacted tax rates in effect for the year in which those temporary differences are expected to be recovered or settled.

For periods prior to the Spin-Out, the Company recognized the benefit of an uncertain tax position that it has taken on income tax returns prepared under a separate return method if such tax position is more likely than not to be sustained on examination by the taxing authorities, based on the technical merits of the position. These tax benefits are measured based on the largest benefit that has a greater than 50% likelihood of being realized upon ultimate resolution. Unrecognized tax benefits related to net operating loss carryforwards or tax credit carryforwards were presented as a reduction to the related gross deferred tax assets in the pre-Spin-Out period. A liability for unrecognized tax benefits is classified as non-current unless the liability is expected to be settled in cash within 12 months of the reporting date.

Certain deferred tax assets and liabilities and uncertain tax positions that arose as a result of Ikaria's past activities, such as federal and state net operating loss carryforwards, research and development credit carryforwards and acquired in-process research and development, were not transferred to the Company in connection with the Spin-Out and continued to constitute assets and liabilities of Ikaria subsequent to the date of the Spin-Out.

As of December 31, 2014 and 2013, the Company had no material uncertain tax positions.

(i) Research and Development Expense

Research and development costs are expensed as incurred. These expenses include the costs of the Company's proprietary research and development efforts, as well as costs incurred in connection with certain licensing arrangements. Upfront and milestone payments made to third parties in connection with research and development collaborations are expensed as incurred up to the point of regulatory approval. Payments made to third parties upon or subsequent to regulatory approval are capitalized and amortized over the remaining useful life of the related product. The Company also expenses the cost of purchased technology and equipment in the period of purchase if it believes that the technology or equipment has not demonstrated technological feasibility and it does not have an alternative future use. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and are recognized as research and development expense as the related goods are delivered or the related services are performed.

(j) New Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update No. 2014-09, or ASU 2014-09, Revenue from Contracts with Customers (Topic 606). ASU 2014-09 supersedes the revenue recognition requirements in Accounting Standards Update No. 2009-13, Revenue Recognition (Topic 605) and requires entities to recognize revenue in a way that depicts the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled to in exchange for those goods or services. ASU 2014-09 is effective for annual reporting periods beginning after December 15, 2016, including interim periods within that reporting period, and is to be applied either retrospectively to each prior reporting period presented or retrospectively with the cumulative effect recognized at the date of initial application. Early application is not permitted. Although the Company does not

generate revenues currently, management is in the process of evaluating the potential impact from the adoption of this guidance.

In June 2014, the FASB issued Accounting Standards Update No. 2014-10, or ASU 2014-10, Development Stage Entities (Topic 915): Elimination of Certain Financial Reporting Requirements, Including an Amendment to Variable Interest Entities Guidance in Topic 810, Consolidation. ASU 2014-10 eliminates the distinction of a development stage entity as well as certain related disclosure requirements, including the elimination of inception-to-date information on the statements of operations, members' equity and cash flows. For public business entities, the amendments in ASU 2014-10 are effective prospectively for annual reporting periods beginning after December 15, 2014, and interim periods within those annual periods, and for other entities, the amendments are effective for annual reporting periods beginning after December 15, 2014, and interim reporting periods beginning after December 15, 2015. Early application is permitted. The Company has adopted ASU 2014-10 for the year ended December 31, 2014.

In June 2014, the FASB issued Accounting Standards Update No. 2014-12, or ASU 2014-12, Compensation—Stock Compensation (Topic 718): Accounting for Share-Based Payments When the Terms of an Award Provide That a Performance Target Could Be Achieved after the Requisite Service Period. ASU 2014-12 clarifies the proper method of accounting for share-based payments when the terms of an award provide that a performance target could be achieved after the requisite service period. ASU 2014-12 requires that a performance target that affects vesting and that could be achieved after the requisite service period be treated as a performance condition. The performance target should not be reflected in estimating the grant-date fair value of the award. Compensation cost should be recognized in the period in which it becomes probable that the performance target will be achieved and should represent the compensation cost attributable to the period(s) for which the requisite service has already been rendered. The amendments in ASU 2014-12 are effective for annual periods and interim periods within those annual periods beginning after December 15, 2015. Earlier adoption is permitted. The Company will adopt this guidance if and when share-based awards with performance targets are issued.

In August 2014, the FASB issued Accounting Standards Update No. 2014-15, or ASU 2014-15, Presentation of Financial Statements—Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern. ASU 2014-15 should reduce diversity in the timing and content of footnote disclosures. ASU 2014-15 requires management to assess an entity's ability to continue as a going concern by incorporating and expanding upon certain principles that are currently in U.S. auditing standards. Specifically, it (1) provides a definition of the term substantial doubt, (2) requires an evaluation every reporting period including interim periods, (3) provides principles for considering the mitigating effect of management's plans, (4) requires certain disclosures when substantial doubt is alleviated as a result of consideration of management's plans, (5) requires an express statement and other disclosures when substantial doubt is not alleviated, and (6) requires an assessment for a period of one year after the date that the financial statements are issued (or available to be issued). The amendments in ASU 2014-15 are effective for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. Early application is permitted. The Company is currently evaluating the impact the adoption of ASU 2014-15 will have on its financial statements.

(3) Liquidity

In the course of its development activities, the Company has sustained operating losses and expects such losses to continue over the next several years. The Company's ultimate success depends on the outcome of its research and development activities. As of December 31, 2014, the Company has an accumulated deficit of approximately $54.2 million. Management expects to incur additional losses in the future to conduct product research and development.

In connection with the Spin-Out, $80.0 million of cash was distributed to the Company. At the time of the Spin-Out, $18.5 million of the $80.0 million cash held by the Company was deposited in escrow to

guarantee payment of the monthly services fees payable by the Company to Ikaria in exchange for the services to be provided by Ikaria pursuant to the transition services agreement during the 24 months following the Spin-Out. The remaining escrowed cash has been classified as restricted cash as of December 31, 2014. See Note 11—*Related-Party Transactions*.

The Company received net proceeds of $52.6 million in February 2015 as a result of the IPO, after deducting underwriting discounts and commissions of $4.2 million and offering costs of $3.2 million. These proceeds, together with the Company's cash and restricted cash on hand, is expected to be sufficient to satisfy the Company's operating cash needs at least into mid-2016. After this time, management recognizes the Company will need to raise additional capital through the potential issuance of additional equity or borrowings or entering into strategic alliances with partner companies to fund all necessary research and development activities to successfully commercialize its product candidates. However, if such additional capital is not available at adequate levels or such strategic alliances do not occur, the Company will need to evaluate its plans. The Company's estimates and assumptions may prove to be wrong, and the Company may exhaust its capital resources sooner than expected. The process of testing product candidates in clinical trials is costly, and the timing of progress in clinical trials is uncertain. Because the Company's product candidates are in clinical development and the outcome of these efforts is uncertain, the Company cannot estimate the actual amounts that will be necessary to successfully complete the development and commercialization, if approved, of its product candidates or whether, or when, the Company may achieve profitability.

(4) Restructuring Charges

In December 2011, Ikaria announced the planned closure of its Seattle-based facility. Charges of $1.3 million were allocated to the Company and recorded in 2011. Accrued severance and related charges were paid in 2012. Facility lease obligations extended through March 2014. In 2012, an additional $0.3 million charge was recorded for the impairment of fixed assets related to the closure of the Seattle-based facility, which was recorded in other operating expense in the 2012 statement of operations and comprehensive loss.

(5) Property, Plant and Equipment

At the date of the Spin-Out, Ikaria transferred specifically identified assets to the Company at the carrying amount of the assets as of February 12, 2014. Prior to the date of the Spin-Out, property, plant and equipment and accumulated depreciation were either specifically identified or allocated to the Company by Ikaria. Property and equipment as of December 31, 2014 and December 31, 2013 consist of the following (in thousands):

	December 31, 2014	December 31, 2013
Machinery, equipment and furniture	$ 2,943	$ 2,943
Less accumulated depreciation	(1,247)	(859)
	$ 1,696	$ 2,084

(6) Other Current Liabilities

Other current liabilities as of December 31, 2013 either specifically identified or allocated to the Company by Ikaria consisted of the following accrued expenses (in thousands):

Other current liabilities — allocated current portion of Ikaria special dividend bonus payable	$ 1,839

See Note 8—*Stock-Based Compensation*, for a discussion of the Ikaria special dividend bonus payable.

No similar liabilities existed at December 31, 2014.

(7) Income Taxes

Although the Company was a limited liability company as of December 31, 2014 and was not subject to income taxes in any jurisdiction, one of the Company's subsidiaries is a C-corporation and is subject to state and federal income taxes. Each member was responsible for the tax liability, if any, related to his, her or its proportionate share of the Company's pre-tax loss. There was an immaterial operating loss in the Company's C-corporation subsidiary in 2014. Accordingly, no provision or benefit for income taxes is reflected in the Company's 2014 consolidated financial statements.

Prior to the date of the Spin-Out, the Company did not file a separate tax return as the Company was included in the tax groupings of other Ikaria entities within the respective entity's tax jurisdiction. As such, the income tax provisions for 2013 and 2012 were calculated using the separate return method, as if the Company filed a separate tax return in each of its respective tax jurisdictions. The income tax provisions for 2013 and 2012 included in these carve out financial statements reflects Ikaria's status as a C-corporation. A reconciliation of the statutory federal income tax rate to the Company's effective tax rate for the years ended December 31, 2013 and 2012 is as follows:

	Year Ended December 31, 2013	Year Ended December 31, 2012
U.S. federal statutory rate	35.0%	35.0%
State and local taxes, net of federal tax effect	5.3%	5.2%
Research tax credits	5.0%	5.6%
Valuation allowance	(44.4)%	(44.6)%
Incentive stock options	(0.1)%	(0.2)%
Other	(0.8)%	(1.0)%
	0.0%	0.0%

Deferred taxes as of December 31, 2013 and 2012 reflect the tax effects of the differences between the amounts recorded as assets and liabilities for financial reporting purposes and the comparable amounts recorded for income tax purposes. Significant components of the deferred tax assets (liabilities) at December 31, 2013 are as follows, as allocated by Ikaria (in thousands):

	December 31, 2013	
	Assets	(Liabilities)
Net operating loss carryforwards	$ 62,295	$ —
Research tax credit carryforwards	9,615	—
Property, plant and equipment	—	(1,269)
Intangible assets	5,140	—
Accrued compensation	1,103	—
Other	28	—
Subtotal	78,181	(1,269)
Valuation allowance	(76,912)	—
Total deferred tax assets (liabilities)	$ 1,269	$ (1,269)
Net deferred tax assets	$ 0	

A valuation allowance is provided when it is more likely than not that some portion or all of the deferred tax assets will not be realized. As of December 31, 2013, management believed that it was more likely than not that the deferred tax assets would not be realized, based on future operations, consideration of tax strategies and the reversal of deferred tax liabilities. As of December 31, 2013, the Company had gross deferred tax assets of $78.2 million. The Company maintained a valuation allowance of $76.9 million at December 31, 2013.

As of December 31, 2013, the Company had unrecognized tax benefits related to research tax credit carryforwards, which were reflected as a reduction to the gross deferred tax asset. As of December 31, 2014 and 2013, the Company had no material uncertain tax positions.

Deferred taxes arising from the loss in the Company's C-corporation subsidiary were fully reserved as of December 31, 2014 and were immaterial. No other deferred taxes existed at December 31, 2014 due to the Company's limited liability company structure.

(8) Stock-Based Compensation

Determining the appropriate fair value of stock-based awards requires the input of subjective assumptions, including the fair value of the Company's units and for options, the expected life of the option and expected volatility. The Company uses the Black-Scholes-Merton option pricing model to value its stock option awards. The assumptions used in calculating the fair value of stock-based awards represent management's best estimates and involve inherent uncertainties and the application of management's judgment. As a result, if factors change and management uses different assumptions, stock-based compensation expense could be materially different for future awards. The expected term of stock options is estimated using the "simplified method," as the Company has no historical information to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock options grants. The simplified method is based on the average of the vesting tranches and the contractual life of each grant. For volatility, the Company uses comparable public companies as a basis for its expected volatility to calculate the fair value of option grants. The risk-free interest rate is based on U.S. Treasury notes with a term approximating the expected term of the option. The estimation of the number of stock awards that will ultimately vest requires judgment, and to the extent actual results or updated estimates differ from the Company's current estimates, such amounts will be recorded as an adjustment in the period in which estimates are revised.

Bellerophon 2014 Equity Incentive Plan

During the year ended December 31, 2014, the Company adopted the 2014 Equity Incentive Plan, or the 2014 Plan, which provides for the grant of options. The Company is authorized to issue options in an amount up to an aggregate of 558,851 non-voting units to eligible employees, directors and consultants, subject to the Board approval and amendments. The granted awards generally have a vesting period of four years, of which 25% of the awards vest on the second anniversary of grant date, 25% vest on the third anniversary and the remaining 50% vest on the fourth anniversary of the grant date.

During the year ended December 31, 2014, the Company awarded a total of 514,266 options to its executives and employees to purchase the equivalent number of non-voting units with an exercise price of $13.28 per unit. Options for non-voting units are granted to employees at exercise prices equal to the fair value of the Company's non-voting units based on an independent third-party appraisal report. Approximately 90,000 options granted were fully vested at the grant date, with the remaining options to vest over a four year period from the date of the Spin-Out. Compensation expense is measured based on the fair value of the option on the grant date and is recognized on a straight-line basis over the requisite service period, or sooner if vesting occurs

sooner than on a straight-line basis. Options are forfeited if the employee ceases to be employed by the Company prior to vesting.

The following are the assumptions used in estimating the fair value of options issued during the year ended December 31, 2014.

	Year Ended December 31, 2014
Valuation assumptions:	
Risk-free interest rate	1.71%
Expected volatility	90.00%
Expected term (in years)	6.1
Expected dividend yield	0.00%

The weighted average grant date fair value of options granted during the year ended December 31, 2014 subsequent to the date of the Spin-Out was $9.90 per option.

A summary of option activity under the 2014 Plan for the year ended December 31, 2014 subsequent to the date of the Spin-Out is presented below:

	Shares	Exercise Price	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (in years)
Options outstanding as of February 12, 2014	—		—	
Granted	514,266	$ 13.28	$ 13.28	
Exercised	—			
Forfeited	(5,986)	13.28	13.28	
Options outstanding as of December 31, 2014	508,280	13.28	13.28	9.5
Options vested and exercisable as of December 31, 2014	90,082	$ 13.28	$ 13.28	9.5

As of December 31, 2014, there was approximately $3.5 million of total unrecognized compensation expense related to non-vested options. This expense is expected to be recognized over a weighted-average period of approximately 3.5 years.

Ikaria Equity Incentive Plans for Periods Prior to February 12, 2014

The Company presented allocated stock-based compensation expenses from Ikaria for the periods prior to February 12, 2014, the date of Spin-Out in its consolidated statements of operations and comprehensive loss. These allocated expenses were derived from Ikaria's historical financial statements. See Note 2(a)—*Summary of Significant Accounting Policies—Basis of Presentation*. The following disclosures for dates prior to the date of the Spin-Out pertain to stock-based compensation and the Ikaria special dividend bonus payable that were allocated to the Company related to Ikaria stock-based awards.

In February 2014, prior to the Spin-Out, each Ikaria stock option, other than options held by non-accredited investors who were also not employees of Ikaria, was adjusted such that it became an option to acquire the same number of shares of Ikaria non-voting common stock as were subject to the Ikaria stock option, or an Adjusted Ikaria Option, and an option to acquire the same number of non-voting limited liability company units of the Company as the number of shares of Ikaria non-voting common stock that were subject to the Ikaria stock option, or a Bellerophon Option. There were 618,212 Bellerophon Options issued as a result of the

adjustment of Ikaria stock options. The vesting of each Adjusted Ikaria Option and Bellerophon Option was fully accelerated on the date of the Spin-Out and all related compensation expense was recognized as an expense by Ikaria.

Ikaria Special Dividend Plan

In October 2011, Ikaria approved dividend equivalent rights for options, restricted stock units, or RSUs, and other equity awards granted under its equity award plans. Pursuant to the special dividend plan, in the event that the Ikaria board declared a dividend, each employee of the Company who held equity awards was eligible to receive a cash payment equal to the amount of the dividend per share, multiplied by the number of equity awards outstanding. The payment was payable as of the declaration date for vested options. For unvested options and unvested RSUs, payment was due upon vesting. As of December 31, 2013, the Company's allocated portion of the special dividend bonus payable was $6.1 million of which $1.8 million was reflected in other current liabilities and $4.3 million was reflected in non-current liabilities. The entire allocated portion of the special dividend bonus payable as of February 11, 2014 was settled in cash on the Company's behalf by Ikaria.

Stock Options

Prior to and in connection with the Spin-Out, the exercise price of each Adjusted Ikaria Option and Bellerophon Option was adjusted by allocating the relative post Spin-Out estimated fair values of Ikaria and the Company in a ratio of 85% and 15%, respectively, to the original Ikaria option exercise price. The expiration date of the options was not modified. The Company's allocable portion of Ikaria's stock-based compensation expense related to options for the period from January 1, 2014 through February 11, 2014 and the year ended December 31, 2013 was approximately $0.1 million and $1.7 million, respectively.

There were 577,975 Bellerophon options outstanding as of December 31, 2014 at exercise prices ranging from $0.26 to $17.92 per unit. All options outstanding were fully vested at the time of the Spin-Out.

A summary of option activity related to the Bellerophon Options for the year ended December 31, 2014 is presented below:

	Ikaria Equity Incentive Plans for Periods Prior to February 12, 2014			
	Shares	Range of Exercise Price	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life (in years)
Options issued and vested at date of Spin-Out as of February 12, 2014	618,212	$ 0.26 - 17.92	$ 7.24	
Granted	—			
Exercised	(8,182)	7.77 - 8.77	7.99	
Forfeited	(32,055)	7.77 - 14.91	9.39	
Options outstanding, vested and exercisable as of December 31, 2014	577,975	$ 0.26 - 17.92	$ 7.11	4.5

Restricted Stock Units

In February 2014, prior to the Spin-Out, each Ikaria RSU was adjusted such that it became an RSU with respect to the same number of shares of Ikaria non-voting common stock as were subject to the Ikaria RSU, or an Adjusted Ikaria RSU, and an RSU with respect to the same number of non-voting limited liability company units of the Company as were subject to the Ikaria RSU, or a Bellerophon RSU. In connection with the Merger and the Spin-Out, the vesting of each Adjusted Ikaria RSU and Bellerophon RSU was fully accelerated. The

compensation expense incurred upon the acceleration of the RSUs was recognized by Ikaria. Fully vested Bellerophon RSUs of 372,947 became Bellerophon non-voting units as of the date of the Spin-Out.

Ikaria had granted RSUs to employees that generally vested over a four-year period. RSUs granted prior to January 1, 2011 vested 25% annually. RSUs granted on and after January 1, 2011 vested 25% on the second and third anniversary of the date of grant and 50% on the fourth anniversary of the date of grant. Shares of Ikaria non-voting common stock were delivered to the employee upon vesting, subject to payment of applicable withholding taxes, which were paid in cash or an equivalent amount of shares withheld. Compensation expense for all RSUs was based on the grant date fair value of the RSU issued, which was based on the fair value of common stock of Ikaria. Compensation expense for RSUs was recognized by Ikaria on a straight-line basis over the requisite service period. The RSU expense allocated from Ikaria totaled $0.2 million for the period from January 1, 2014 through February 11, 2014.

Stock-Based Compensation Expense, Net of Estimated Forfeitures

The following table summarizes the stock-based compensation expense by the consolidated statement of operations and comprehensive loss line item for the years ended December 31, 2014, 2013 and 2012. For comparison purposes, the following disclosures include stock-based compensation expense recognized under the 2014 Plan and stock-based compensation expense for dates prior to the Spin-Out that were allocated to the Company related to Ikaria stock-based awards.

	Year Ended December 31,		
(in thousands)	2014	2013	2012
Research and development	$ 271	$ 1,120	$ 882
General and administrative	1,568	601	567
Total expense	$ 1,839	$ 1,721	$ 1,449
Tax benefit	—	(232)	(140)
Expense, net of tax benefit	$ 1,839	$ 1,489	$ 1,309

(9) Investment by Ikaria, Inc.

The Company's historical operating cash requirements prior to the date of the Spin-Out were provided by Ikaria. The balance in the investment by Ikaria account as of the date of the Spin-Out of $177.5 million represented the investment by Ikaria in the Company, including cash funding as well as the impact of stock-based compensation awards, which increased equity, and the Ikaria special dividend bonus payable allocated to the Company, which decreased equity. This amount was eliminated with the transfer of net assets at the date of the Spin-Out.

(10) Product Acquisitions and Other Agreements

The Company has entered, and will consider entering, into agreements to develop and commercialize product candidates, which may include research and development, marketing and selling, manufacturing and distribution agreements. These agreements often require milestone and royalty or profit share payments, contingent upon the occurrence of certain future events linked to the success of the asset in development, as well as expense reimbursements. Costs incurred pursuant to these agreements are reported in their respective expense line items in the statements of operations.

BioLineRx Ltd.

In August 2009, the Company entered into a license agreement with BioLineRx Ltd. and BioLine Innovations Jerusalem L.P., which are referred to collectively as BioLine, under which the Company obtained an exclusive worldwide license to BCM. The Company paid BioLine a $7.0 million upfront payment in 2009 and a $10.0 million milestone payment in 2010.

Under the terms of the license agreement, the Company is obligated to use commercially reasonable efforts to develop and commercialize at least one product containing BCM. Under the terms of the license agreement, if the Company achieves certain clinical and regulatory events specified in the license agreement, the Company will be obligated to pay milestone payments to BioLine that could total, in the aggregate, up to $115.5 million, and if the Company achieves certain commercialization targets specified in the license agreement, the Company will be obligated to pay additional milestone payments to BioLine that could total, in the aggregate, up to $150.0 million. In addition, the Company is obligated to pay BioLine a specified percentage of any upfront consideration it receives for sublicensing BCM, as well as royalties on net sales, if any, at a percentage ranging from 11% to 15%, depending on net sales level, of any approved product containing BCM, subject to offsets for specified payments to third parties made in connection with BCM. The Company's obligation to pay BioLine royalties will expire on a product-by-product and country-by-country basis on the date on which BCM is no longer covered by a valid claim in the licensed patent rights in the given country.

BioLine has the option, exercisable under specified circumstances, to manufacture any product containing BCM for the Company pursuant to terms to be negotiated by the parties. If BioLine exercises this option, the Company would generally be obligated to purchase at least a specified percentage of its BCM requirements from BioLine at a price calculated using a pre-agreed methodology.

Except under specified circumstances, the Company may not directly or indirectly acquire more than a specified percentage of the equity or debt securities of BioLine, or urge, induce, entice or solicit any other party to acquire such securities, without BioLine's consent.

The Company and BioLine have the right to terminate the license agreement for an uncured material breach by the other party. In addition, the Company has the right to terminate the license agreement if at any time the Company determines that further development of products containing BCM is not warranted. See Note 13—*Commitments and Contingencies*.

(11) Related-Party Transactions

Separation and Distribution Agreement

In connection with the Spin-Out, in February 2014, the Company and Ikaria entered into a separation and distribution agreement which sets forth provisions relating to the separation of the Company's business from Ikaria's other businesses. The separation and distribution agreement described the assets and liabilities that remained with or were transferred to the Company and those that remained with or were transferred to Ikaria. The separation and distribution agreement provides for a full and complete release and discharge of all liabilities between Ikaria and the Company, except as expressly set forth in the agreement. The Company and Ikaria each agreed to indemnify, defend and hold harmless the other party and its subsidiaries, and each of their respective past and present directors, officers and employees, and each of their respective permitted successors and assigns, from any and all damages relating to, arising out of or resulting from, among other things, the Company's business and certain additional specified liabilities or Ikaria's business and certain additional specified liabilities, as applicable.

License Agreement

In February 2014, the Company entered into a cross-license, technology transfer and regulatory matters agreement with a subsidiary of Ikaria. Pursuant to the terms of the license agreement, Ikaria granted to the Company a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights controlled by Ikaria to engage in the development, manufacture and commercialization of nitric oxide, devices to deliver nitric oxide and related services for or in connection with out-patient, chronic treatment of patients who have PAH, PH-COPD or idiopathic pulmonary fibrosis, or PH-IPF. Pursuant to the terms of the license agreement, the Company granted Ikaria a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights that the Company controls to engage in the development, manufacture and commercialization of products and services for or used in connection with the diagnosis, prevention or treatment, whether in- or out-patient, of certain conditions and diseases other than PAH, PH-COPD or PH-IPF and for the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital. The Company agreed that, during the term of the license agreement, it will not, without the prior written consent of Ikaria, grant a sublicense under any of the intellectual property licensed to the Company under the license agreement to any of its affiliates or any third party, in either case, that directly or indirectly competes with Ikaria's nitric oxide business.

Agreements Not to Compete

In September 2013, October 2013 and February 2014, the Company and each of its subsidiaries entered into an agreement not to compete with a subsidiary of Ikaria, or, collectively, the agreements not to compete. Pursuant to the agreements not to compete, the Company and each of its subsidiaries agreed not to engage, anywhere in the world, in any manner, directly or indirectly, until the earlier of five years after the effective date of such agreement not to compete or the date on which Ikaria and all of its subsidiaries are no longer engaged in such business, in:

- the development, manufacture, commercialization, promotion, sale, import, export, servicing, repair, training, storage, distribution, transportation, licensing, or other handling or disposition of any product or service (including, without limitation, any product or service that utilizes, contains or includes nitric oxide for inhalation, a device intended to deliver nitric oxide or a service that delivers or supports the delivery of nitric oxide), bundled or unbundled, for or used in connection with (a) the diagnosis, prevention, or treatment, in both adult and/or pediatric populations, and whether in- or out-patient, of: (i) hypoxic respiratory failure associated with pulmonary hypertension, (ii) pulmonary hypertensive episodes and right heart failure associated with cardiovascular surgery, (iii) bronchopulmonary dysplasia, (iv) the management of ventilation—perfusion mismatch in acute lung injury, (v) the management of ventilation—perfusion mismatch in acute respiratory distress syndrome, (vi) the management of pulmonary hypertension episodes and right heart failure in congestive heart failure, (vii) pulmonary edema from high altitude sickness, (viii) the management of pulmonary hypertension episodes and right heart failure in pulmonary or cardiac surgery, (ix) the management of pulmonary hypertension episodes and right heart failure in organ transplant, (x) sickle cell vaso-occlusive crisis, (xi) hypoxia associated with pneumonia, or (xii) ischemia-reperfusion injury, or (b) the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital; or

- any and all development, manufacture, commercialization, promotion, sale, import, export, storage, distribution, transportation, licensing, or other handling or disposition of any terlipressin or any other product within the pressin family, (a) intended to treat (i) hepatorenal syndrome in any form (HRS), (ii) bleeding esophageal varices or (iii) septic shock or (b) for or in connection with the management of low blood pressure.

Transition Services Agreement

In February 2014, the Company and Ikaria entered into the TSA, pursuant to which Ikaria agreed to use commercially reasonable efforts to provide certain transition services to the Company for a twenty-four month term, which services include management/executive, human resources, real estate, information technology, accounting, financial planning and analysis, legal, quality and regulatory support. Ikaria also has agreed to use reasonable efforts to provide the Company with the use of office space at Ikaria's headquarters in Hampton, New Jersey pursuant to the terms of the TSA. In exchange for the services, beginning in February 2014, the Company is obligated to pay Ikaria monthly services fees in the amount of $772,000 plus out of pocket expenses and certain other expenses. At the time of the Spin-Out, the Company deposited the sum of $18.5 million, representing the aggregate of the $772,000 monthly service fees payable by the Company under the TSA, in escrow to guarantee payment of the monthly services fees by the Company. The escrowed cash is classified as restricted cash as of December 31, 2014. The Company recorded expenses of $8.2 million from the date of the Spin-Out through December 31, 2014 in connection with the TSA. At December 31, 2014, the Company had accrued expenses due to Ikaria of $0.5 million in connection with the TSA.

Supply Agreements

In February 2014, the Company entered into drug supply and device supply agreements with a subsidiary of Ikaria. Under these agreements, Ikaria agreed to use commercially reasonable efforts to supply inhaled nitric oxide and nitric oxide delivery devices for use in the Company's clinical trials, in each case at Ikaria's manufacturing cost plus a 20% mark-up, and in the case of the drug supply agreement, the Company has agreed to purchase its clinical supply of inhaled nitric oxide from Ikaria. The Company also granted Ikaria a right of first negotiation in the event that the Company desires to enter into a commercial supply agreement with a third party for supply of nitric oxide for inhalation. The amount due to Ikaria under the drug supply agreement as of December 31, 2014 was approximately $0.2 million. The device supply agreement expired on February 9, 2015 and no amounts were due to Ikaria under this agreement as of December 31, 2014.

(12) Segments and Geographic Information

The Company operates in one reportable segment and solely within the United States. Accordingly, no segment or geographic information has been presented.

(13) Commitments and Contingencies

Legal Proceedings

The Company periodically becomes subject to legal proceedings and claims arising in connection with its business. The ultimate legal and financial liability of the Company in respect to all proceedings, claims and lawsuits, pending or threatened, cannot be estimated with any certainty.

BioLine previously indicated to the Company that it believed that the Company had breached the license agreement in several ways, including, but not limited to, failure to use commercially reasonable efforts to develop BCM, failure to provide BioLine with material information concerning the development and commercialization plans for BCM and failure to notify BioLine in advance of material public disclosures regarding BCM. The Company and BioLine also previously disagreed about the timing of a certain milestone payment that the Company would owe BioLine based upon progress in the Company's BCM clinical development program. The Company believed it had complied with its obligations under the license agreement to use commercially reasonable efforts to develop BCM and was not in breach of its other obligations under the license agreement. No amounts were previously accrued for this matter since no loss was probable as of December 31, 2014. On January 8, 2015, the Company and BioLine agreed to amend the license agreement, which resolved the prior disputes and provided for a release of claims by BioLine. The amendment also changed certain milestones and related payments, but the total potential milestone payments to be paid to BioLine under the license agreement remained the same. No additional milestones have been met as of March 31, 2015.

As of the date of this report, there is no proceeding, claim or litigation, pending or threatened, that could, individually or in the aggregate, have a material adverse effect on the Company's business, operating results, financial condition and/or liquidity.

Operating Lease and Transition Services Agreement

The Company leases an operating facility located in North Brunswick, New Jersey under an operating lease arrangement. Future minimum rental commitments under the Company's non-cancellable operating lease and future required payments under the TSA as of December 31, 2014 are as follows (in thousands):

	Operating Lease(1)	Transition Services Agreement (2)
2015	$ 23	$ 9,264
Thereafter	—	1,548
Total	$ 23	$ 10,812

(1) Reflects the Company's obligation to make payments in connection with a lease for its operating facilities. The amounts in the table do not include the Company's rent obligation of $115,000 from March 15, 2015 through March 15, 2016 under an extension to the Company's lease that the Company signed subsequent to December 31, 2014.

(2) See Note 11—*Related Party Transactions* for a description of the TSA.

Rent expense, including direct and allocated expenses, is calculated on the straight-line basis and amounted to approximately $0.5 million for each of the years ended December 31, 2014, 2013 and 2012.

(14) Net Loss Per Unit

Basic net loss per unit is calculated by dividing net loss by the weighted average number of units outstanding during the period. Diluted net loss per unit is calculated by dividing net loss by the weighted average number of units outstanding, adjusted to reflect potentially dilutive securities (options) using the treasury stock method, except when the effect would be anti-dilutive. No net loss per unit information is presented for periods prior to the Spin-Out.

The weighted average units outstanding for basic and diluted net loss per unit for the for the year ended December 31, 2014 was 7,898,289, which represents the weighted average number of units outstanding for the period from February 12, 2014 through December 31, 2014.

The Company is reporting a net loss for the year ended December 31, 2014, therefore diluted net loss per unit is the same as the basic net loss per unit.

As of December 31, 2014, the Company had 1,086,255 options to purchase units outstanding that have been excluded from the computation of diluted weighted average units outstanding, because such securities had an antidilutive impact due to the loss reported.

(15) Subsequent Events

Effective as of January 1, 2015, the Company entered into a services agreement with Ikaria, or the 2015 Services Agreement, pursuant to which the Company has agreed to use commercially reasonable efforts to provide certain services to Ikaria, including services related to regulatory matters, drug and device safety, clinical operations, biometrics and scientific affairs. In connection with the execution of the 2015 Services Agreement, Ikaria paid the Company a one-time service fee in the amount of $916,666 and will be obligated to pay the Company a service fee in the amount of $83,333 per month for 13 months, subject to performance of the services. In addition, pursuant to the terms and conditions of the 2015 Services Agreement, Ikaria has agreed to use commercially reasonable efforts to provide certain services to the Company, including services related to information technology, and servicing and upgrades of INOpulse devices. The Company is obligated to pay Ikaria certain fees under the 2015 Services Agreement that total, in the aggregate, approximately $215,000, subject to termination of the 2015 Services Agreement. The 2015 Services Agreement will terminate in February 2016.

On February 2, 2015, the Company effected a reverse unit split of its outstanding units at a ratio of one unit for every 12.5257 units previously held. All unit and per unit data included in these consolidated financial statements reflect the reverse unit split.

On February 12, 2015, the Company converted from a Delaware limited liability company to a Delaware corporation in connection with the IPO.

On February 19, 2015, the Company completed the sale of 5,000,000 shares of common stock in the IPO at a price to the public of $12.00 per share, resulting in net proceeds to the Company of $52.6 million after deducting underwriting discounts and commissions of $4.2 million and offering costs of $3.2 million. The Company's common stock began trading on the NASDAQ Global Market under the symbol "BLPH" on February 13, 2015.

On March 5, 2015, Mallinckrodt plc and Ikaria announced that the two companies had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria and that they expect the acquisition will be completed in the second calendar quarter of 2015. While the Company's TSA, license agreement and drug supply agreement impose binding obligations on Ikaria to perform in accordance with such agreements' terms, it is possible that following completion of the sale, as the new owner's influence on Ikaria's operations increases, Ikaria may not continue to provide the same level of performance under such agreements as it has provided to date, or may perform differently than it has to date. Moreover, to the extent that the Company desires to extend or renew the TSA or expand the scope of the TSA, license agreement or drug supply agreement, it is also possible that Ikaria will not be willing to do so on reasonable terms, or at all.

(16) Quarterly Financial Data (unaudited)

	Three Months Ended December 31,		Three Months Ended September 30,		Three Months Ended June 30,		Three Months Ended March 31,	
(in thousands, except unit and per unit data)	2014	2013	2014	2013	2014	2013	2014	2013
Operating expenses:								
Research and development	$ 9,610	$ 13,917	$ 11,559	$ 11,762	$ 12,769	$ 14,959	$ 12,040	$ 12,347
General and administrative	3,177	2,857	3,934	2,549	4,194	1,838	2,470	1,769
Total operating expenses	12,787	16,774	15,493	14,311	16,963	16,797	14,510	14,116
Interest income	18	—	13	—	48	—	—	—
Total other income	18	—	13	—	48	—	—	—
Pre-tax loss	(12,769)	(16,774)	(15,480)	(14,311)	(16,915)	(16,797)	(14,510)	(14,116)
Income tax benefit (expense)	—	—	—	—	—	—	—	—
Net loss and comprehensive loss	$ (12,769)	$ (16,774)	$ (15,480)	$ (14,311)	$ (16,915)	$ (16,797)	$ (14,510)	$ (14,116)
Weighted average units outstanding:								
Basic and diluted	7,898,922		7,897,143		7,898,301		7,899,251	
Net loss per unit:								
Basic and diluted	$ (1.62)		$ (1.96)		$ (2.14)		$ (1.84)	

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2014. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, or persons performing similar functions, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2014, our principal executive officer and principal financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for "emerging growth companies."

Changes in Internal Control Over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the fiscal quarter ended December 31, 2014 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Executive Officers, Key Employees and Directors

The following table sets forth the name, age and position of each of our executive officers, key employees and directors as of March 25, 2015.

Name	Age	Position
Jonathan M. Peacock	57	Chief Executive Officer, President and Chairman of the Board
Manesh Naidu	45	Vice President and Chief Business Officer
Reinilde Heyrman, M.D.	54	Vice President, Chief Clinical Development Officer and Secretary
Martin Meglasson, Ph.D.	65	Vice President and Chief Scientific Officer
David Abrams	40	Treasurer
Deborah A. Quinn, M.D.	60	Vice President and Medical Lead for INOpulse Programs
Martin Dekker	42	Vice President of Device Engineering
Matthew Holt(2)(3)	38	Director
Jens Luehring(1)	41	Director
Andre V. Moura(1)(3)	33	Director
Robert T. Nelsen(2)	51	Director
Daniel Tassé	55	Director
Adam B. Weinstein(1)	36	Director

(1) Member of the Audit Committee

(2) Member of the Compensation Committee

(3) Member of the Nominating and Corporate Governance Committee

Jonathan M. Peacock has served as our Chief Executive and President and as the Chairman of our board of directors since June 2014. Prior to joining us, Mr. Peacock served as the Chief Financial Officer of Amgen Inc., a biotechnology company, from September 2010 to January 2014. From November 2005 to September 2010, he served as Chief Financial and Administrative Officer of Novartis Pharmaceuticals AG, the Pharmaceuticals and Biotechnology division of Novartis AG. Mr. Peacock was a partner at McKinsey and Company, a global strategy consulting firm, from 1998 to 2005. Before that, he was a partner at Price Waterhouse LLP, a global accounting firm (now PricewaterhouseCoopers LLP), from 1993 to 1998. He currently serves on the board of directors of Kite Pharma, Inc., a biopharmaceutical company. Mr. Peacock received an M.A. degree in economics from the University of St. Andrews. We believe that Mr. Peacock is qualified to serve on our board of directors because of his global management experience, his experience as an officer of a public company in our industry, his financial expertise and his position as our Chief Executive Officer and President.

Manesh Naidu has served as our Vice President and Chief Business Officer since February 2014. Mr. Naidu previously served as Vice President and General Manager of the INOpulse program of Ikaria, a biotherapeutics company, from August 2011 to February 2014, and prior to that, he served as Senior Director, Marketing Strategy of Ikaria from May 2008 to August 2011. Prior to joining Ikaria, Mr. Naidu held several positions at Novartis Corporation and Pfizer Inc., both of which are pharmaceutical companies, from 2003 to 2008. He also worked at McKinsey & Company, a global strategy consulting firm, from 2001 to 2003. Mr. Naidu received an M.S. in chemical engineering from Oklahoma State University, a B.E. in chemical engineering and an M.S. in chemistry both from the Birla Institute of Technology and Science, and an M.B.A. from the Kellogg School of Management at Northwestern University.

Reinilde Heyrman, M.D. has served as our Vice President, Chief Clinical Development Officer and Secretary since February 2014. Prior to joining us, Dr. Heyrman served as Vice President, Chief Clinical Development Officer of Ikaria from March 2012 to February 2014. Dr. Heyrman held several positions at Daiichi Sankyo Pharma Development, a pharmaceutical company, from 2005 to March 2012, most recently as Vice President, Clinical Development from 2009 to March 2012. From 2001 to 2002 and 2002 to 2005, Dr. Heyrman served as Director Clinical Research and Senior Director Clinical Research, respectively, at Sankyo Pharma Development, a pharmaceutical company. Dr. Heyrman received an M.D. from the University of Antwerp, Belgium.

Martin Meglasson, Ph.D. has served as our Vice President and Chief Scientific Officer since February 2014. From July 2010 to February 2014, Dr. Meglasson served as Chief Scientific Officer of Ikaria. Prior to joining Ikaria, Dr. Meglasson served as Vice President, head of Research and Development of Ligand Pharmaceuticals Incorporated, a biotechnology company, from February 2004 to July 2010. From 1996 to 2003, Dr. Meglasson was Director of Preclinical Pharmacology at Pharmacia, Inc., a pharmaceutical company, and from 1984 to 1992, he was first an Assistant Professor and later an Associate Professor of Pharmacology at the University of Pennsylvania School of Medicine. Dr. Meglasson received a B.S. in biology, an M.S. in physiology and a Ph.D. in pharmacology, each from the University of Houston.

David Abrams has served as our Treasurer since February 2014, with responsibilities for treasury, financial planning and financial reporting. Prior to joining us, Mr. Abrams held various roles in strategic financial planning at Ikaria from October 2010 to February 2014 and at Johnson & Johnson, a healthcare products company, from May 2002 to October 2010. Mr. Abrams has previously held roles at Stern Stewart and Deutsche Bank. Mr. Abrams received a B.S. in economics from The Wharton School of Business of the University of Pennsylvania and a B.A. in history from the University of Pennsylvania.

Deborah A. Quinn, M.D. has served as our Vice President and Medical Lead for the INOpulse programs since January 2015. Prior to joining us, Dr. Quinn held several positions at Novartis Pharmaceuticals AG from December 2006 to January 2015, most recently as medical director for both pulmonary arterial hypertension and heart failure programs. Previously, Dr. Quinn worked at the Massachusetts General Hospital from 1998 to 2011 where she was an Instructor in Medicine from 1998 to 2006 and a Clinical Assistant Professor in Medicine at Harvard Medical School from 2006 to 2011. Her postdoctoral training in Medicine and Pulmonary and Critical Care Fellowship were at Massachusetts General Hospital. She received an M.D. from the University of Massachusetts Medical School.

Martin Dekker has served as our Vice President of Device Engineering since January 2015. Prior to joining us, Mr. Dekker held several positions at Spacelabs Healthcare, a company that develops and manufacturers medical devices, from November 1998 to January 2015, most recently as Director of Global Operations Engineering. During his time at Spacelabs Healthcare, Mr. Dekker led and co-designed new products, developed and launched transformative manufacturing technologies and championed cross-functional quality/engineering projects. He is a member of the Institute of Electrical and Electronic Engineers. Mr. Dekker received a B.S. in electronics from Noordelijke Hogeschool Leeuwarden, the Netherlands.

Matthew Holt has served as a member of our board of directors since February 2014. Since 2001, Mr. Holt has been employed by New Mountain Capital, a private equity group, where he currently serves as a Managing Director. Prior to joining New Mountain Capital, Mr. Holt served in the mergers and acquisitions Group at Lehman Brothers, a financial services firm. Mr. Holt has served on the board of directors of Ikaria since March 2007. Mr. Holt received an A.B. in English and American literature and language from Harvard College. We believe that Mr. Holt is qualified to serve on our board of directors because of his financial expertise and his years of experience providing strategic advisory services across many industries.

Jens Luehring has served as a member of our board of directors since January 2015. Mr. Luehring has been the Head of Finance, Americas, of The Linde Group since April 2012. In this position, his responsibilities include accounting, tax, business planning, investments, treasury and insurance. Prior to his current role,

Mr. Luehring was the Head of Mergers & Acquisitions of The Linde Group from April 2007 to March 2012. Mr. Luehring received a Master of Business Economics from Hanover University in 1998. Prior to joining The Linde Group in January 2006, Mr. Luehring worked in investment banking, covering corporate finance, private equity, equity capital markets and mergers and acquisitions. We believe that Mr. Luehring is qualified to serve on our board of directors because of his financial, business and strategic expertise.

Andre V. Moura has served as a member of our board of directors since February 2014. Mr. Moura joined New Mountain Capital in 2005, where he currently serves as a Director. Prior to joining New Mountain Capital, Mr. Moura was employed by McKinsey & Company, a global management consulting firm. Mr. Moura also serves on the board of directors of two privately held companies. Mr. Moura received an A.B. in computer science from Harvard College and an M.B.A. from Harvard Business School. We believe that Mr. Moura is qualified to serve on our board of directors because of his financial expertise and his years of experience providing strategic advisory services to diverse companies across multiple industries.

Robert T. Nelsen has served as a member of our board of directors since February 2014. Since 1986, Mr. Nelsen has served as a Co-Founder and Managing Director of ARCH Venture Partners, a venture capital firm focused on early-stage technology companies. Mr. Nelsen currently serves as a director of Agios Pharmaceuticals, Inc., Fate Therapeutics, Inc., Kythera Biopharmaceuticals, Inc. and Sage Therapeutics, Inc., each a publicly traded biopharmaceutical company. Mr. Nelsen previously served as a director of Adolor Corporation, Array BioPharma Inc., Illumina, Inc., NeurogesX, Inc., Receptos, Inc. and Trubion Pharmaceuticals, Inc., each a biopharmaceutical company. Mr. Nelsen also serves on the board of several privately held companies, including Sapphire Energy Corporation. Mr. Nelsen received a B.S. from the University of Puget Sound, with majors in biology and economics, and an M.B.A. from the University of Chicago Graduate School of Business. We believe that Mr. Nelsen is qualified to serve on our board of directors because of his extensive experience with biotechnology companies, his financial expertise and his years of experience providing strategic and financial advisory services to pharmaceutical and biotechnology organizations, including evaluating business plans involving clinical trials.

Daniel Tassé has served as a member of our board of directors since February 2014 and served as our Chairman from February 2014 to June 2014. Since January 2008, Mr. Tassé has served as President and Chief Executive Officer and as a member of the board of directors of Ikaria. Mr. Tassé was appointed chairman of Ikaria's board of directors in October 2009. Mr. Tassé served as our Interim Chief Executive Officer and President from February 2014 to June 2014. From October 2004 to January 2008, Mr. Tassé served as General Manager of the Pharmaceuticals and Technologies Business Unit of Baxter International, Inc., a global diversified healthcare company. From July 2001 to October 2004, Mr. Tassé served as Vice President and Regional Director for Australasia at GlaxoSmithKline, a healthcare company. Mr. Tassé currently serves as a director of Indivior PLC, a publicly traded company, and serves on its audit and compensation committees. Mr. Tassé is a member of the Healthcare Leadership Council and a member of the board of directors of the Roundtable on Critical Care Policy. He also is a member of the board of directors and health section governing board of the Biotechnology Industry Organization, where he participates on the bioethics, regulatory environment and reimbursement committees. Additionally, Mr. Tassé is a member of the board of directors of the Pharmaceutical Research and Manufacturers Association of America, where he participates on the FDA and biomedical research committee. Mr. Tassé received a B.S. in biochemistry from the University of Montreal. We believe Mr. Tassé is qualified to serve on our board of directors because of his former service as our Chief Executive Officer and President, his extensive track record of business building in the healthcare industry, his strong background within critical care, his global management experience and his detailed knowledge of the pharmaceutical industry, our company, employees, client base and competitors.

Adam B. Weinstein has served as a member of our board of directors since February 2014. He is a Managing Director of New Mountain Capital, LLC, and he joined that organization in 2005. At New Mountain, Mr. Weinstein serves as a Chief Financial Officer and is an Executive Vice President and is on the Board of Directors of New Mountain Finance Corporation, a publicly traded business development company. Prior to joining New Mountain, Mr. Weinstein held roles in the mergers and acquisitions and private equity investor

services areas of Deloitte & Touche, LLP, in that firm's merger and acquisition and private equity investor services areas. Mr. Weinstein is a New York State Certified Public Accountant and received his B.S., summa cum laude, in accounting from Binghamton University. We believe that Mr. Weinstein is qualified to serve on our board of directors because of his financial and accounting expertise and valuable corporate governance experience.

There are no family relationships among any of our directors or executive officers.

Audit Committee and Audit Committee Financial Expert

Our board of directors has established an audit committee, which operates under a charter that has been approved by our board of directors. The members of our audit committee are Messrs. Luehring, Moura and Weinstein. Mr. Weinstein chairs our audit committee. In addition, our board of directors has determined that Mr. Weinstein is an "audit committee financial expert" as defined in applicable SEC rules.

The rules established by the NASDAQ Stock Market, or NASDAQ rules, require that, subject to specified exceptions, each member of a listed company's audit committee be independent and that audit committee members also satisfy independence criteria set forth in Rule 10A-3 under the Exchange Act. In order to be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors or any other board committee, accept, directly or indirectly, any consulting, advisory or other compensatory fee from the listed company or any of its subsidiaries or otherwise be an affiliated person of the listed company or any of its subsidiaries. The phase-in periods with respect to director independence under the applicable NASDAQ rules allow us to have only one independent member on the audit committee upon the listing date of our common stock, which in our case was February 13, 2015, a majority of independent members on the audit committee within 90 days of the listing date and a fully independent audit committee within one year of the listing date.

Our board of directors has determined that Mr. Luehring, who is a member of our audit committee, satisfies the independence standards for the audit committee established by the SEC and NASDAQ rules, including, the independence requirements of Rule 10A-3 under the Exchange Act. Our board of directors has determined that neither Mr. Moura nor Mr. Weinstein is currently independent under Rule 10A-3 of the Exchange Act, but determined that Mr. Moura will be permitted to remain on the audit committee for a period of up to 90 days following the listing date and Mr. Weinstein will be permitted to remain on the audit committee for a period of up to one year following the listing date, in each case in accordance with the phase-in period under NASDAQ rules.

Our audit committee assists our board of directors in its oversight of our accounting and financial reporting process and the audits of our financial statements. Our audit committee's responsibilities include:

- appointing, approving the compensation of, and assessing the independence of our registered public accounting firm;
- overseeing the work of our independent registered public accounting firm, including through the receipt and consideration of reports from such firm;
- reviewing and discussing with management and our independent registered public accounting firm our annual and quarterly financial statements and related disclosures;
- monitoring our internal control over financial reporting, disclosure controls and procedures and code of business conduct and ethics;
- overseeing our internal audit function;
- overseeing our risk assessment and risk management policies;

- establishing policies regarding hiring employees from our independent registered public accounting firm and procedures for the receipt and retention of accounting related complaints and concerns;
- meeting independently with our internal auditing staff, our independent registered public accounting firm and management;
- reviewing and approving or ratifying any related person transactions; and
- preparing the audit committee report required by SEC rules.

All audit and non-audit services, other than *de minimis* non-audit services, to be provided to us by our independent registered public accounting firm must be approved in advance by our audit committee.

Code of Ethics and Code of Conduct

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of the code on our website, www.bellerophon.com. If we make any substantive amendments to, or grant any waivers from, the code of business conduct and ethics for any officer or director, we will disclose the nature of such amendment or waiver on our website or in a current report on Form 8-K.

Section 16(a) Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our directors and certain officers and holders of more than 10% of our common stock to file with the SEC initial reports of ownership of our common stock and other equity securities on a Form 3 and reports of changes in such ownership on a Form 4 or Form 5. These Section 16 reporting persons are required by SEC regulations to furnish us with copies of all Section 16(a) forms they file. However, during the fiscal year ended December 31, 2014, we did not have any class of equity security registered under Section 12 of the Exchange Act, accordingly no reports were required to be filed pursuant to Section 16(a) by these Section 16 reporting persons with respect to our common stock during that fiscal year.

Item 11. Executive Compensation

This section describes the material elements of compensation awarded to, earned by or paid to each of our named executive officers. We were formed on October 17, 2013 as a subsidiary of Ikaria and we became an independent, stand-alone operating company as a result of the Spin-Out on February 12, 2014. Because the costs and liabilities with respect to compensation of our employees for the fiscal year ended December 31, 2013 and for prior periods were paid by Ikaria on the basis of criteria and methodology not relevant to us and work performed with respect to businesses in addition to ours, we are not presenting compensation information for historical periods.

In connection with becoming a public company, we have begun a thorough review of all elements of our executive compensation program, including the function and design of our equity incentive programs. We have begun to, and expect to continue to in the coming months, evaluate the need for revisions to our executive compensation program to ensure that our program is competitive with the companies with which we compete for executive talent and is appropriate for a public company. As we gain experience as a stand-alone, public company, we expect that the specific direction, emphasis and components of our executive compensation program will continue to evolve. Moving forward, our compensation committee will review and approve the compensation of our executive officers and oversee and administer our executive compensation programs and initiatives.

2014 Summary Compensation Table

The following table sets forth information regarding compensation earned by Jonathan Peacock, our President and Chief Executive Officer, Daniel Tassé, our former interim Chief Executive Officer, Reinilde Heyrman, our Chief Clinical Development Officer, and Martin Meglasson, our Chief Scientific Officer, during our fiscal year ended December 31, 2014. We refer to Mr. Peacock, Dr. Heyrman and Dr. Meglasson as our named executive officers.

Name and Principal Position	Salary ($)	Bonus ($)	Option Awards ($)(1)	All Other Compensation ($)	Total ($)
Jonathan Peacock					
President and Chief Executive Officer	201,539	224,000(2)	4,470,833	58,351(3)	4,954,723
Daniel Tassé(4)					
Former Interim Chief Executive Officer	—	—	—	—	—
Reinilde Heyrman					
Chief Clinical Development Officer	366,808	288,720(5)	79,246	—	734,774
Martin Meglasson					
Chief Scientific Officer	307,154	266,160(6)	79,246	—	652,560

(1) The amounts reported in the "Option Awards" column reflect the aggregate fair value of stock-based compensation awarded during the year computed in accordance with the provisions of FASB ASC Topic 718. See Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K regarding assumptions underlying the valuation of equity awards.

(2) Represents amounts earned in 2014 but paid in 2015, of which $112,000 was paid in cash and $112,000 was paid through the grant of stock options, which amount reflects the aggregate fair value of the stock options computed in accordance with FASB ASC Topic 718. See Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on 10-K regarding assumptions underlying the valuation of equity awards.

(3) Consists of $52,197 of relocation costs incurred by us in connection with Mr. Peacock becoming our President and Chief Executive Officer, and $6,154 that we matched pursuant to our 401(k) plan.

(4) In 2014, we did not pay a base salary nor did we make any other awards of compensation to our former interim Chief Executive Officer, Daniel Tassé. Prior to our Spin-Out, Mr. Tassé was compensated by our former parent company, Ikaria, of which he continues to serve as President and Chief Executive Officer.

(5) Includes $138,720 earned in 2014 but paid in 2015, of which $69,360 was paid in cash and $69,360 was paid through the grant of stock options, which amount reflects the aggregate fair value of the stock options computed in accordance with FASB ASC Topic 718. See Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on 10-K regarding assumptions underlying the valuation of equity awards.

(6) Includes $116,160 earned in 2014 but paid in 2015, of which $58,080 was paid in cash and $58,080 was paid through the grant of stock options, which amount reflects the aggregate fair value of the stock options computed in accordance with FASB ASC Topic 718. See Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on 10-K regarding assumptions underlying the valuation of equity awards.

Narrative to Summary Compensation Table

Base Salary. In 2014, we paid salaries of $201,539 to Mr. Peacock, $366,808 to Dr. Heyrman and $307,158 to Dr. Meglasson. On an annualized basis, the 2014 base salaries of our named executive officers were: $400,000 to Mr. Peacock, $433,500 to Dr. Heyrman and $363,000 to Dr. Meglasson. Base salaries are used to recognize the experience, skills, knowledge and responsibilities required of all of our employees, including our executive officers. We did not engage in any form of benchmarking in the determination of base salaries of our executive officers. Our compensation committee will review the salaries of our executives annually at the beginning of each calendar year and recommend to our board of directors changes in salaries based primarily on changes in job responsibilities, experience, individual performance and comparative market data. We will pay our named executive officers the following annualized base salaries for the year ending December 31, 2015: $400,000 to Mr. Peacock, $433,500 to Dr. Heyrman and $363,000 to Dr. Meglasson.

Bonus Compensation. Our named executive officers are expected to be eligible to receive an annual bonus award in accordance with the management incentive program then in effect with respect to such executive officer and based on an annualized target of base salary. Our named executive officers are also expected to be eligible for performance-based annual bonus awards based on metrics to be determined by our board of directors, in consultation with the executive officer, and our board of directors will determine the extent to which the metrics have been satisfied and the amount of the annual bonus, if any. The performance-based bonuses are designed to motivate our employees to achieve annual goals based on our strategic, financial and operating performance objectives.

On February 3, 2014, we delivered a letter to Dr. Heyrman and to Dr. Meglasson offering them each a one-time $150,000 “retention bonus” payment if she or he remained an active employee of Bellerophon in good standing through December 19, 2014. We paid these retention bonus payments, less applicable taxes, to Dr. Heyrman and Dr. Meglasson in December 2014.

With respect to 2014, the compensation committee awarded total bonus compensation, paid in 2015 partially in cash and partially in stock options, with a value of $224,000 to Mr. Peacock, $138,720 to Dr. Heyrman and $116,160 to Dr. Meglasson. The cash portion of each named executive officer’s bonus was: $112,000 to Mr. Peacock, $69,360 to Dr. Heyrman and $58,080 to Dr. Meglasson. The remaining portion of each named executive officer’s bonus amount was paid through the grant of stock options in the following amounts: 16,000 shares to Mr. Peacock, 9,909 shares to Dr. Heyrman and 8,297 shares to Dr. Meglasson.

Long-Term Equity Based Incentive Awards. We believe that equity grants provide our executives with a strong link to our long-term performance, create an ownership culture and help to align the interests of our executives and our stockholders. In addition, we believe that equity grants with a time-based vesting feature promote executive retention because this feature incentivizes our named executive officers to remain in our employment during the vesting period. Accordingly, our compensation committee and board of directors periodically review the equity incentive compensation of our named executive officers and from time to time may grant additional equity incentive awards to them in the form of stock options.

Outstanding Equity Awards at 2014 Fiscal Year-End

The following table sets forth information regarding outstanding stock options held by our named executive officers and Mr. Tassé as of December 31, 2014:

	Option Awards			
Name	Number of Securities Underlying Unexercised Options Exercisable (#)	Number of Securities Underlying Unexercised Options Unexercisable (#)	Option Exercise Price ($)	Option Expiration Date
Jonathan Peacock	90,082	360,329(1)	$ 13.28	6/20/2024
Daniel Tassé	35,926	—	$ 7.77	12/16/2019
	59,876	—	$ 10.40	1/20/2018
Reinilde Heyrman	—	7,983(2)	$ 13.28	6/20/2024
Martin Meglasson	7,983	—	$ 7.77	12/07/2020
	—	7,983(2)	$ 13.28	6/20/2024

(1) This option vested as to 20% of the underlying shares on June 20, 2014 and vests as to an additional 20% of the underlying shares annually thereafter through June 20, 2018.

(2) This option vests as to (i) 25% of the underlying shares on February 12, 2016, (ii) 25% of the underlying shares on February 12, 2017 and (iii) 50% of the underlying shares on February 12, 2018.

In connection with the Spin-Out, Ikaria distributed our then outstanding units to its stockholders through the payment of a special dividend on a pro rata basis based on each stockholder's ownership of Ikaria capital stock. Prior to the Spin-Out, we issued to certain employees and directors of ours and of Ikaria, including certain of our executive officers, options to purchase the same number of our non-voting membership units as the number of shares of non-voting Ikaria stock subject to the Ikaria options then held by such employee or director at such time. The vesting of these options was subsequently accelerated and all are now fully vested.

Employment Agreements with Our Executive Officers

Agreement with Mr. Peacock

In June 2014, we entered into an employment agreement with Mr. Peacock in connection with the commencement of his employment with us. The agreement provides that Mr. Peacock is employed at will, and either we or Mr. Peacock may terminate the employment relationship for any reason, at any time. Mr. Peacock is required to give us at least 30 days' prior notice if he elects to terminate his employment other than for good reason (as defined in the employment agreement). Following the end of each calendar year, Mr. Peacock is eligible to receive an annual bonus for such calendar year in accordance with the terms of our management incentive program, calculated as a percentage of his annual base salary. As of the date of this Annual Report on Form 10-K, Mr. Peacock's target bonus percentage is 100%. In March 2015, we entered into an amendment with Mr. Peacock to his employment agreement to provide that, beginning with the 2014 annual bonus and for years thereafter, we, in our sole discretion, may pay such bonus compensation in cash, equity or a combination thereof on such terms as are determined by the compensation committee.

If we terminate Mr. Peacock's employment without cause (as defined in the employment agreement) or if Mr. Peacock terminates his employment with us for good reason (as defined in the employment agreement), Mr. Peacock is entitled to receive: (1) a lump sum payment in an amount equal to earned but unpaid base salary through the date of his termination of employment and any unpaid annual bonus that was earned by Mr. Peacock and declared due and owing by us, any accrued but unpaid vacation time, and any incurred but unreimbursed expenses, together with any other benefits to which Mr. Peacock is entitled under our benefit plans and arrangements; and (2) subject to his continued compliance with the restrictive covenants of the agreement and his execution and nonrevocation of a general release of claims against us: (a) a pro-rated portion of his annual

bonus target for the year in which his employment terminates, payable in a single lump sum; (b) payments for a period of 18 months following the date of termination in an aggregate amount equal to one and one half times the sum of (i) Mr. Peacock's annual base salary and (ii) the greater of his applicable annual bonus target and the actual annual bonus most recently paid to Mr. Peacock, determined on a monthly basis; and (c) continued coverage, under our medical, dental and vision benefit plans at active-employee rates for 18 months following the date of termination.

We have agreed to indemnify and hold Mr. Peacock harmless from and against any liabilities Mr. Peacock may incur under Section 409A of the Internal Revenue Code of 1986, as amended, on account of any payments made to Mr. Peacock pursuant to his employment agreement.

Mr. Peacock is subject to confidentiality, invention assignment, non-competition and non-solicitation obligations pursuant to the terms of his employment agreement.

Agreements with Other Named Executive Officers

We also have written employment agreements with Dr. Heyrman and Dr. Meglasson. Each agreement provides for an employment term of one year, with the term automatically renewing for successive one-year terms, unless we or the applicable officer gives written notice of non-renewal at least 90 days prior to the renewal date. Each of these officers is subject to confidentiality, invention assignment, non-competition and non-solicitation agreements.

In addition, for each calendar year, each executive officer named below is eligible to receive an annual bonus in accordance with the terms of our management incentive program. The bonus is calculated as a percentage of the executive's annual base salary. As of the date of this Annual Report on Form 10-K, the target bonus percentage for each such executive officer is as follows: Dr. Heyrman 40% and Dr. Meglasson 40%. In order to receive her bonus, Dr. Heyrman must be employed by us at the time the bonus is declared due and owing. In March 2015, we entered into an amendment with each of Dr. Heyrman and Dr. Meglasson to her or his respective employment agreement to provide that, beginning with the 2014 annual bonus and for years thereafter, we, in our sole discretion, may pay such bonus compensation in cash or a combination of cash and equity, in each instance on such terms as are determined by the compensation committee; provided, however, that if the annual bonus is to be paid in a combination of cash and equity, such cash and equity components will be in equal parts. In addition, Dr. Meglasson's employment agreement amendment provided that if Dr. Meglasson's employment is terminated by us for any reason other than for cause on or after the date that he reaches age 65 or if Dr. Meglasson retires on after the date that he reaches age 67, then any stock options then held by him will continue to vest and be exercisable after his employment is terminated on the same vesting schedule as if he remained employed by us.

Both Dr. Heyrman and Dr. Meglasson are entitled to severance payments if her or his employment is terminated under specified circumstances.

Dr. Reinilde Heyrman. If we terminate Dr. Heyrman's employment without cause (as defined in the employment agreement), Dr. Heyrman terminates her employment with us for good reason (as defined in the employment agreement) or Dr. Heyrman terminates her employment at the end of a term following delivery by us of notice that we will not extend the term, Dr. Heyrman is entitled to receive: (1) a lump sum payment in an amount equal to earned but unpaid base salary through the date of termination of her employment and any unpaid annual bonus that was earned by Dr. Heyrman and declared due and owing by us and any accrued but unpaid vacation time, together with any other benefits to which Dr. Heyrman is entitled under our benefit plans and arrangements; and (2) subject to her continued compliance with the restrictive covenants of the employment agreement and her execution and nonrevocation of a general release of claims against us: (a) payments for a period of 12 months following the date of termination in an aggregate amount equal to the sum of (i) Dr. Heyrman's annual base salary and (ii) the greater of her applicable annual bonus target and the actual annual bonus most recently paid to Dr. Heyrman, determined on a monthly basis; and (b) continued coverage, under our medical, dental and vision benefit plans at active employee rates for 12 months following the date of termination.

In the event that we terminate Dr. Heyrman's employment without cause, Dr. Heyrman terminates her employment with us for good reason, or Dr. Heyrman terminates her employment at the end of a term following delivery by us of notice that we will not extend the term, in each case within 12 months of the occurrence of a change in control (as defined in the employment agreement), any equity compensation granted to Dr. Heyrman shall become fully vested as of the date of termination.

Dr. Martin Meglasson. If we terminate Dr. Meglasson's employment without cause (as defined in the employment agreement), Dr. Meglasson terminates his employment with us for good reason (as defined in the employment agreement) or Dr. Meglasson terminates his employment at the end of a term following delivery by us of notice that we will not extend the term, Dr. Meglasson is entitled to receive: (1) a lump sum payment in an amount equal to earned but unpaid base salary through the date of his termination of employment and any unpaid annual bonus that was earned by Dr. Meglasson and declared due and owing by us and any accrued but unpaid vacation time, together with any other benefits to which Dr. Meglasson is entitled under our benefit plans and arrangements; and (2) subject to his continued compliance with the restrictive covenants of the agreement and his execution and nonrevocation of a general release of claims against us: (a) a pro-rated portion of his annual bonus target for the year in which his employment terminates, payable in a single lump sum, and payments for a period of 12 months following the date of termination in an aggregate amount equal to the sum of (i) Dr. Meglasson's annual base salary and (ii) the greater of his applicable annual bonus target and the actual annual bonus most recently paid to Dr. Meglasson, determined on a monthly basis; and (b) continued coverage, under our medical, dental and vision benefit plans at active-employee rates for 12 months following the date of termination.

In the event that we terminate Dr. Meglasson's employment without cause, Dr. Meglasson terminates his employment with us for good reason or Dr. Meglasson terminates his employment at the end of a term following delivery by us of notice that we will not extend the term, in each case within 18 months of, or in certain circumstances related to a potential change in control prior to, the occurrence of a change in control, Dr. Meglasson is entitled to receive, in addition to the payments and benefits described in the preceding paragraph and subject to his continued compliance with the restrictive covenants of the employment agreement and his execution and nonrevocation of a general release of claims against us: (a) a lump sum payment in an amount equal to 50% of the sum of (i) Dr. Meglasson's annual base salary and (ii) the greater of his annual bonus target and the actual annual bonus most recently paid to Dr. Meglasson; (b) an additional six months of continued coverage under our medical, dental and vision benefit plans at active employee rates; and (c) the unvested portion of any equity compensation granted to Dr. Meglasson shall become immediately fully vested.

We have agreed to indemnify and hold Dr. Meglasson harmless from and against any liabilities Dr. Meglasson may incur under 409A of the Internal Revenue Code of 1986, as amended, on account of any payments made to Dr. Meglasson pursuant to his employment agreement.

Stock Option and Other Compensation Plans

The four equity incentive plans described in this section are (i) the assumed 2007 Ikaria stock option plan, which we refer to as the 2007 Ikaria plan, (ii) the assumed Ikaria 2010 long term incentive plan, which we refer to as the 2010 Ikaria plan, (iii) our 2014 equity incentive plan and (iv) our 2015 equity incentive plan. Following the effectiveness of the registration statement for our initial public offering, we will grant awards to eligible participants only under the 2015 equity incentive plan.

Assumed 2007 Ikaria Plan

The 2007 Ikaria plan was adopted by Ikaria in March 2007, and we assumed the terms of the 2007 Ikaria plan in connection with the Spin-Out. Stock options granted under the 2007 Ikaria plan have a contractual life of ten years. Pursuant to the terms of the 2007 Ikaria plan, in the event of a liquidation or dissolution of our company, each outstanding option under the 2007 Ikaria plan will terminate immediately prior to the consummation of the action, unless the administrator determines otherwise. In the event of a merger or other reorganization event, each outstanding option will be assumed or an equivalent option or right will be substituted by the successor entity, unless such successor entity does not agree to assume the award or to substitute an equivalent option or right in which case such option will terminate upon the consummation of the merger or reorganization event.

Assumed 2010 Ikaria Plan

The 2010 Ikaria plan was adopted by Ikaria in February 2010 and amended and restated in May 2010, and we assumed the terms of the 2010 Ikaria plan in connection with the Spin-Out. Pursuant to the terms of the 2010 Ikaria plan, upon our liquidation, dissolution, merger or consolidation, except as otherwise provided in an applicable option or award agreement, each option or award will be (i) treated as provided in the agreement related to the transaction, or (ii) if not so provided in such agreement, each holder of an option or award will be entitled to receive, in respect of each share subject to outstanding options or awards, the same number of stock, securities, cash, property or other consideration that he or she would have received had he or she exercised such options or awards prior to the transaction. The stock, securities, cash, property or other consideration shall remain subject to all of the conditions, restrictions and performance criteria which were applicable to the options and awards prior to any such transaction. If the consideration paid or distributed is not entirely shares of common stock of the acquiring or resulting corporation, the treatment of outstanding options and stock appreciation rights may include the cancellation of outstanding options and stock appreciation rights upon consummation of the transaction as long as the holders of affected options and stock appreciation rights, at the election of the compensation committee, either:

- have been given a period of at least 15 days prior to the date of the consummation of the transaction to exercise the options or stock appreciation rights (whether or not they were otherwise exercisable); or

- are paid (in cash or cash equivalents) in respect of each share covered by the option or stock appreciation right being cancelled an amount equal to the excess, if any, of the per share price paid or distributed to stockholders in the transaction (the value of any non-cash consideration to be determined by the compensation committee in its sole discretion) over the exercise price of the option or stock appreciation right.

2014 Equity Incentive Plan

In June 2014, our board of directors adopted, and our stockholders approved, the 2014 equity incentive plan. The 2014 equity incentive plan is administered by our board of directors or by a committee appointed by our board of directors. The 2014 equity incentive plan provides for the grant of options. As of December 31, 2014, there were 50,571 shares of non-voting common stock available for the grant of options under the 2014 equity incentive plan.

Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2014 equity incentive plan. Subject to any limitation in the 2014 equity incentive plan, our board of directors or any committee to which our board of directors has delegated authority will select the recipients of options and determine:

- the number of shares of non-voting common stock covered by options, the dates upon which those options become exercisable and the terms and conditions that apply to such options;

- the exercise price of options which may not be less than 100% of the fair market value of our non-voting common stock on the grant date;

- the duration of options, which may not be in excess of ten years;

- the methods of payment of the exercise price of options; and

- any amendments to the 2014 equity incentive plan and/or any option agreement.

Our board of directors may exercise such powers and perform such acts as it deems necessary or expedient to promote the best interests of our company which are not in conflict with the 2014 equity incentive plan provisions.

Awards under the 2014 equity incentive plan are subject to adjustment in the event of a split, reverse split, dividend, recapitalization, combination or reclassification of Company common stock, spin-off or other similar change in our capitalization or event or any dividend or distribution to holders of our common stock other than an ordinary cash dividend.

Upon a merger or other reorganization event (as defined in the 2014 equity incentive plan), our board of directors, may, in its sole discretion, take any one or more of the following actions pursuant to the 2014 equity incentive plan, as to some or all outstanding options:

- provide that all outstanding options will be assumed, or substantially equivalent awards shall be substituted, by the acquiring or successor corporation or an affiliate thereof;
- upon written notice to a participant, provide that the participant's unvested and/or unexercised options will terminate immediately prior to the consummation of such transaction unless exercised by the participant;
- provide that outstanding options will become exercisable, realizable or deliverable, or restrictions applicable to an option will lapse, in whole or in part, prior to or upon the reorganization event;
- in the event of a reorganization event pursuant to which holders of shares of non-voting common stock will receive a cash payment for each share of non-voting common stock surrendered in the reorganization event, make or provide for a cash payment to the participants with respect to each option held by the participant equal to (1) the number of shares of non-voting common stock subject to the vested portion of the option, after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event, multiplied by (2) the excess, if any, of the cash payment for each share of non-voting common stock surrendered in the reorganization event over the exercise price of such option and any applicable tax withholdings, in exchange for the termination of such option; and
- provide that, in connection with a liquidation or dissolution, options convert into the right to receive liquidation proceeds.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2014 equity incentive plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.

Our board of directors may amend, suspend or terminate the 2014 equity incentive plan at any time, except that stockholder approval will be required to comply with applicable law or stock market requirements.

2015 Equity Incentive Plan

In January 2015, our board of directors adopted, and in February 2015, our stockholders approved, the 2015 equity incentive plan, which became effective immediately prior to the effectiveness of the registration statement for our initial public offering. The 2015 equity incentive plan provides for the grant of incentive stock options, nonstatutory stock options, share appreciation rights, restricted share awards, restricted share unit awards and other share-based awards. Upon the effectiveness of the 2015 equity incentive plan, the number of shares of our common stock that were reserved for issuance under the 2015 equity incentive plan was equal to the sum of (1) 449,591 plus (2) the number of shares (up to 558,851 shares) equal to the sum of the number of shares of our common stock available for issuance under the 2014 equity incentive plan immediately prior to the

effectiveness of the registration statement for our initial public offering and the number of shares of our common stock subject to outstanding awards under the 2014 equity incentive plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right plus (3) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2016 and continuing until, and including, the fiscal year ending December 31, 2025, equal to the least of (i) 798,358 shares of our common stock, (ii) a number equal to the difference between 5% of the number of shares of our common stock outstanding on the first day of the fiscal year (treating all shares of our common stock issuable upon the exercise of outstanding options and upon the conversion of outstanding shares of preferred stock, warrants or other securities convertible into shares of our common stock as outstanding for this purpose) and the number of shares of our common stock available for grant under the 2015 equity incentive plan on the first day of the fiscal year and (iii) an amount determined by our board of directors. Solely for purposes of the 2015 equity incentive plan, from and after the Corporate Conversion until the closing of our initial public offering "shares of our common stock" referred to shares of our non-voting common stock. Upon the closing of our initial public offering, "shares of our common stock" shall refer to shares of our voting common stock and awards granted prior to the closing of our initial public offering automatically became awards covering shares of our voting common stock at such time.

Our employees, officers, directors, consultants and advisors are eligible to receive awards under the 2015 equity incentive plan. However, incentive stock options may only be granted to our employees. We granted options to purchase an aggregate of 99,367 shares to certain of our employees upon the commencement of trading of our common stock on the NASDAQ Global Market under the 2015 equity incentive plan.

Pursuant to the terms of the 2015 equity incentive plan, our board of directors (or a committee delegated by our board of directors) administers the plan and, subject to any limitations in the plan, selects the recipients of awards and determines:

- the number of shares of our common stock covered by options and the dates upon which the options become exercisable;
- the type of options to be granted;
- the duration of options, which may not be in excess of ten years;
- the exercise price of options, which must be at least equal to the fair market value of our common stock on the date of grant;
- the methods of payment of the exercise of options; and
- the number of shares of our common stock subject to and the terms of any share appreciation rights, restricted share awards, restricted share units or other share-based awards and the terms and conditions of such awards, including conditions for repurchase, issue price and repurchase price (though the measurement price of share appreciation rights must be at least equal to the fair market value of our common stock on the date of grant and the duration of such awards may not be in excess of ten years).

If our board of directors delegates authority to an officer to grant awards under the 2015 equity incentive plan, the officer will have the power to make awards to all of our officers, except executive officers. Our board of directors will fix the terms of the awards to be granted by such officer, including the exercise price of such awards (which may include a formula by which the exercise will be determined), and the maximum number of shares subject to awards that such officer may make.

Upon a merger or other reorganization event, our board of directors may, except to the extent specifically provided otherwise in an award or other agreement between us and the plan participant, take any

one or more of the following actions pursuant to the 2015 equity incentive plan as to some or all outstanding awards other than restricted shares:

- provide that all outstanding awards shall be assumed, or substantially equivalent awards shall be substituted, by the acquiring or succeeding corporation (or an affiliate thereof);
- upon written notice to a participant, provide that all of the participant's unvested and/or unexercised awards will terminate immediately prior to the consummation of such reorganization event unless exercised by the participant (to the extent then exercisable) within a specified period;
- provide that outstanding awards shall become exercisable, realizable or deliverable, or restrictions applicable to an award shall lapse, in whole or in part, prior to or upon such reorganization event;
- in the event of a reorganization event pursuant to which holders of shares of our common stock will receive a cash payment for each share surrendered in the reorganization event, make or provide for a cash payment to the participants with respect to each award held by a participant equal to (1) the number of shares of our common stock subject to the vested portion of the award (after giving effect to any acceleration of vesting that occurs upon or immediately prior to such reorganization event) multiplied by (2) the excess, if any, of the cash payment for each share surrendered in the reorganization event over the exercise, measurement or purchase price of such award and any applicable tax withholdings, in exchange for the termination of such award;
- provide that, in connection with a liquidation or dissolution, awards shall convert into the right to receive liquidation proceeds (if applicable, net of the exercise, measurement or purchase price thereof and any applicable tax withholdings); and/or
- any combination of the foregoing.

Our board of directors does not need to take the same action with respect to all awards, all awards held by a participant or all awards of the same type.

In the case of certain restricted share units, no assumption or substitution is permitted, and the restricted share units will instead be settled in accordance with the terms of the applicable restricted share unit agreement.

Upon the occurrence of a reorganization event other than a liquidation or dissolution, the repurchase and other rights with respect to outstanding restricted share awards will continue for the benefit of the successor company and will, unless the board of directors may otherwise determine, apply to the cash, securities or other property into which shares of our common stock are converted or exchanged pursuant to the reorganization event, provided that our board of directors may provide for the termination or deemed satisfaction of such repurchase or other rights under the applicable award agreement or any other agreement between the participant and us. Upon the occurrence of a reorganization event involving a liquidation or dissolution, all restrictions and conditions on each outstanding restricted share award will automatically be deemed terminated or satisfied, unless otherwise provided in the agreement evidencing the restricted share award or in any other agreement between the participant and us.

At any time, our board of directors may, in its sole discretion, provide that any award under the 2015 equity incentive plan will become immediately exercisable in full or in part, free of some or all restrictions or conditions, or otherwise realizable in full or in part.

No award may be granted under the 2015 equity incentive plan on or after February 12, 2025. Our board of directors may amend, suspend or terminate the 2015 equity incentive plan at any time, except that stockholder approval may be required to comply with applicable law or stock market requirements.

401(k) Retirement Plan

We maintain a 401(k) retirement plan that is intended to be a tax-qualified defined contribution plan under Section 401(k) of the Internal Revenue Code. In general, all of our employees are eligible to participate, beginning on the first day of the month following commencement of their employment. The 401(k) plan includes a salary deferral arrangement pursuant to which participants may elect to reduce their current compensation by up to the statutorily prescribed limit, equal to $17,500 in 2014, and have the amount of the reduction contributed to the 401(k) plan.

Limitations on Liability and Indemnification

Our certificate of incorporation limits the personal liability of directors for breach of fiduciary duty to the maximum extent permitted by the Delaware General Corporation Law and provides that no director will have personal liability to us or to our stockholders for monetary damages for breach of fiduciary duty or other duty as a director. However, these provisions do not eliminate or limit the liability of any of our directors:

- for any breach of the director's duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- for voting for or assenting to unlawful payments of dividends, stock repurchases or other distributions; or
- for any transaction from which the director derived an improper personal benefit.

Any amendment to or repeal of these provisions will not eliminate or reduce the effect of these provisions in respect of any act, omission or claim that occurred or arose prior to such amendment or repeal. If the Delaware General Corporation Law is amended to provide for further limitations on the personal liability of directors of corporations, then the personal liability of our directors will be further limited to the greatest extent permitted by the Delaware General Corporation Law.

In addition, our certificate of incorporation provides that we must indemnify our directors and officers and we must advance expenses, including attorneys' fees, to our directors and officers in connection with legal proceedings, subject to very limited exceptions.

In addition, we have entered into indemnification agreements with each of our directors and officers. These indemnification agreements may require us, among other things, to indemnify each such director or officer for some expenses, including attorneys' fees, judgments, fines and settlement amounts incurred by him or her in any action or proceeding arising out of his or her service as one of our directors or officers.

We maintain a general liability insurance policy that covers certain liabilities of our directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers.

Certain of our non-employee directors may, through their relationships with their employers, be insured and/or indemnified against certain liabilities incurred in their capacity as members of our board of directors.

Rule 10b5-1 Sales Plans

Our directors and executive officers may adopt written plans, known as Rule 10b5-1 plans, in which they will contract with a broker to buy or sell shares of our common stock on a periodic basis. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the director or officer when entering into the plan, without further direction from the director or officer. The director or officer may adopt, amend or terminate a plan when not in possession of material, non-public information. In addition, our directors

and executive officers may also buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Director Compensation

In January 2015, our board established the following compensation policy for non-employee directors, which became effective upon the closing of our initial public offering in February 2015:

- each non-employee director receives, on an annual basis, a cash retainer of $30,000;
- each non-employee director who has then served on our board of directors for at least six months will receive, on the date of the first board meeting held after each year's annual meeting of stockholders, an option to purchase 798 shares of our common stock, which shall vest in full on the earlier of the first anniversary of the date of grant or immediately prior to the first annual meeting of stockholders occurring after the date of grant;
- the chairman of our board of directors, if a non-employee director, receives an additional cash retainer of $30,000;
- each non-employee director who serves on the audit committee receives a cash retainer of $7,500 per year ($15,000 for the chair);
- each non-employee director who serves on the compensation committee receives a cash retainer of $5,000 per year ($10,000 for the chair);
- each non-employee director who serves on the nominating and corporate governance committee receives a cash retainer of $3,000 ($7,000 for the chair); and
- each non-employee director elected to the board following the closing of our initial public offering will receive a one-time award of an option to purchase 3,991 shares of our common stock, which option shall vest in three equal annual installments.

In addition, we reimburse our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending board of director and committee meetings.

Prior to our initial public offering in February 2015, we did not have a formal non-employee director compensation policy. We did not compensate any of our current non-employee directors for his service as a director in 2014. We have historically reimbursed our non-employee directors for reasonable travel and out-of-pocket expenses incurred in connection with attending board of director and committee meetings. Jonathan Peacock, one of our directors who also serves as our President and Chief Executive Officer, does not receive any additional compensation for his service as a director. The compensation that we pay to Mr. Peacock for his service as our President and Chief Executive Officer is discussed in the "Executive Compensation" section of this Annual Report on Form 10-K.

The New Mountain Entities have advised us that, in connection with the affiliation of Messrs. Holt, Moura and Weinstein with the New Mountain Entities, all equity based compensation, including grants of stock options in respect of shares of our common stock, received or receivable by Messrs. Holt, Moura and Weinstein in consideration for their services rendered to us will be held by such director for the benefit of New Mountain Capital, L.L.C., an affiliate of the New Mountain Entities. In addition, the New Mountain Entities have advised us that any cash compensation received by such directors in consideration for their services rendered to us will be paid to New Mountain Capital, L.L.C.

Compensation Committee Interlocks and Insider Participation

None of our executive officers serves as a member of the board of directors or compensation committee, or other committee serving an equivalent function, of any other entity that has one or more of its executive officers serving as a member of our board of directors or our compensation committee. None of the members of our compensation committee is, or has ever been, an officer or employee of our company.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

Security Ownership of Certain Beneficial Owners and Management

The following table sets forth information with respect to the beneficial ownership of our common stock as of March 16, 2015 by:

- each person, or group of affiliated persons, who is known by us to beneficially own more than 5% of our common stock;
- each of our named executive officers;
- each of our directors; and
- all of our executive officers and directors as a group.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC and includes voting or investment power with respect to our common stock. Shares of our common stock subject to options that are currently exercisable or exercisable within 60 days of March 16, 2015 are considered outstanding and beneficially owned by the person holding the options for the purpose of calculating the percentage ownership of that person but not for the purpose of calculating the percentage ownership of any other person. Except as otherwise noted, to our knowledge, the persons and entities in this table have sole voting and investing power with respect to all of the shares of our common stock beneficially owned by them, subject to community property laws, where applicable. The information is not necessarily indicative of beneficial ownership for any other purpose.

The percentage ownership calculations for beneficial ownership are based on 12,905,392 shares of common stock outstanding as of March 16, 2015.

Except as otherwise set forth below, the address of the beneficial owner is c/o Bellerophon Therapeutics, Inc., 53 Frontage Road, Suite 301, Hampton, New Jersey 08827.

Name of Beneficial Owner	Number of Shares Beneficially Owned	Percentage of Shares Beneficially Owned
5% Stockholders		
New Mountain Entities(1)	4,859,885	37.7%
Linde(2)	1,629,804	12.6%
Fidelity Investments (FMR LLC)(3)	1,292,882	10.0%
ARCH(4)	965,660	7.5%
Venrock(5)	962,415	7.5%
Executive Officers and Directors		
Jonathan M. Peacock(6)	114,949	*
Manesh Naidu(7)	18,769	*
Reinilde Heyrman(8)	11,960	*
Martin Meglasson(9)	28,443	*
David Abrams(10)	2,237	*
Matthew S. Holt(11)	4,859,885	37.7%
Jens Luehring(12)	1,629,804	12.6%
Andre V. Moura	—	*
Robert Nelsen(13)	965,660	7.5%
Daniel Tassé(14)	224,700	1.7%
Adam B. Weinstein(15)	4,859,885	37.7%
All executive officers and directors as a group (11 persons)(16)	7,856,407	59.9%

* Less than one percent.

(1) Consists of 346,974 shares held by Allegheny New Mountain Partners, L.P., 80,165 shares held by New Mountain Affiliated Investors II, L.P., 3,842,663 shares held by New Mountain Partners II (AIV-A), L.P. and 590,083 shares held by New Mountain Partners II (AIV-B), L.P. The general partner of each of the New Mountain Entities is New Mountain Investments II, L.L.C. and the manager of each of the New Mountain Entities is New Mountain Capital L.L.C. Steven Klinsky is the managing member of New Mountain Investments II, L.L.C. Adam Weinstein, a member of our board of directors, is a member of New Mountain Investments II, L.L.C. Matthew Holt, a member of our board of directors, is a member of New Mountain Investments II, L.L.C. New Mountain Investments II, L.L.C. has decision-making power over the disposition and voting of shares of portfolio investments of each of the New Mountain Entities. New Mountain Capital, L.L.C. also has voting power over the shares of portfolio investments of the New Mountain Entities in its role as the investment advisor. New Mountain Capital, L.L.C. is a wholly-owned subsidiary of New Mountain Capital Group, L.L.C. New Mountain Capital Group, L.L.C. is 100% owned by Steven Klinsky. Since New Mountain Investments II, L.L.C. has decision-making power over the New Mountain Entities, Mr. Klinsky may be deemed to beneficially own the shares that the New Mountain Entities hold of record or may be deemed to beneficially own. Mr. Klinsky, Mr. Weinstein, Mr. Holt, New Mountain Investments II, L.L.C. and New Mountain Capital, L.L.C. disclaim beneficial ownership over the shares held by the New Mountain Entities, except to the extent of their pecuniary interest therein. The address of the New Mountain Entities is c/o New Mountain Capital, L.L.C., 787 Seventh Avenue, 48th Floor, New York, New York 10019.

(2) Consists of 1,629,804 shares held by Linde North America, Inc., an indirect wholly-owned subsidiary of Linde AG. Jens Luehring, a member of our board of directors, is a director and chief financial officer of Linde North America, Inc. Mr. Luehring disclaims beneficial ownership of all shares held by Linde, except to the extent of his pecuniary interest therein, if any. The address of Linde North America, Inc. is 575 Mountain Avenue, Murray Hill, New Jersey 07974.

(3) Based on information provided in a Schedule 13G filed by FMR LLC on March 10, 2015. Edward C. Johnson 3d, a Director and Chairman of FMR LLC, and Abigail P. Johnson, a Director, Vice Chairman, and the Chief Executive Officer of FMR LLC, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, as amended, to form a controlling group with respect to FMR LLC. Neither FMR LLC nor Edward C. Johnson 3d nor Abigail P. Johnson has the sole power to vote or direct the voting of the shares owned directly by the various investment companies registered under the Investment Company Act, which we refer to as the Fidelity Funds, advised by Fidelity Management & Research Company, which we refer to as FMR Co, a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds' Boards of Trustees. FMR Co carries out the voting of the shares under written guidelines established by the Fidelity Funds' Boards of Trustees. FMR LLC reports that it holds sole dispositive power with respect to 1,292,882 shares. The address of FMR LLC is 245 Summer Street, Boston, Massachusetts 02210.

(4) Consists of 965,660 shares held by ARCH Venture Fund VI, L.P., or ARCH VI. ARCH Venture Partners VI, L.P., or the GPLP, as the sole general partner of ARCH VI, may be deemed to beneficially own certain of the shares held of record by ARCH VI. The GPLP disclaims beneficial ownership of all shares held of record by ARCH VI in which the GPLP does not have an actual pecuniary interest. ARCH Venture Partners VI, LLC, or the GPLLC, as the sole general partner of the GPLP, may be deemed to beneficially own certain of the shares held of record by ARCH VI. The GPLLC disclaims beneficial ownership of all shares held of record by ARCH VI in which it does not have an actual pecuniary interest. Keith Crandell, Clinton Bybee and Robert Nelsen, a member of our board of directors, are the managing directors of the GPLLC and may be deemed to beneficially own certain of the shares held of record by ARCH VI. The managing directors disclaim beneficial ownership of all shares held of record by ARCH VI in which they do not have an actual pecuniary interest. ARCH VI reports that it holds shared voting power and shares dispositive power with respect to 965,660 shares. The address of ARCH VI is 8725 West Higgins Road, Suite 290, Chicago, Illinois 60631.

(5) Consists of 783,407 shares held by Venrock Associates IV, L.P.; 159,761 shares that are held by Venrock Partners, L.P. and 19,247 shares that are held by Venrock Entrepreneurs Fund IV, L.P. Venrock Management IV, LLC, Venrock Partners Management, LLC and VEF Management IV, LLC are the sole general partners of Venrock Associates IV, L.P., Venrock Partners, L.P. and Venrock Entrepreneurs Fund IV, L.P., respectively. Venrock Management IV, LLC, Venrock Partners Management, LLC and VEF Management IV, LLC disclaim beneficial ownership of all shares held by Venrock Associates IV, L.P., Venrock Partners, L.P. and Venrock Entrepreneurs Fund IV, L.P., except to the extent of their pecuniary interest therein. The address of Venrock is 3340 Hillview Avenue, Palo Alto, California 94304.

(6) Includes 94,082 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

(7) Includes 7,450 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

(8) Includes 2,477 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

(9) Includes 10,057 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

(10) Consists of 2,237 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

(11) Consists of 346,974 shares held by Allegheny New Mountain Partners, L.P., 80,165 shares held by New Mountain Affiliated Investors II, L.P., 3,842,663 shares held by New Mountain Partners II (AIV-A), L.P. and 590,083 shares held by New Mountain Partners II (AIV-B), L.P. The general partner of each of the New Mountain Entities is New Mountain Investments II, L.L.C. and the manager of each of the New Mountain Entities is New Mountain Capital L.L.C. Matthew Holt, a member of our board of directors, is a member of New Mountain Investments II, L.L.C. New Mountain Investments II, L.L.C. has decision-making power over the disposition and voting of shares of portfolio investments of each of the New Mountain Entities. New Mountain Capital, L.L.C. also has voting power over the shares of portfolio investments of the New Mountain Entities in its role as the investment advisor. New Mountain Capital, L.L.C. is a wholly-owned subsidiary of New Mountain Capital Group, L.L.C. Mr. Holt disclaims beneficial ownership over the shares held by the New Mountain Entities, except to the extent of his pecuniary interest therein.

(12) Consists of 1,629,804 shares held by Linde North America, Inc., an indirect wholly-owned subsidiary of Linde AG. Jens Luehring, a member of our board of directors, is a director and the chief financial officer of Linde North America, Inc. Mr. Luehring disclaims beneficial ownership of all shares held by Linde, except to the extent of his pecuniary interest therein, if any.

(13) Consists of 965,660 shares held by ARCH Venture Fund VI, L.P., or ARCH VI. ARCH Venture Partners VI, L.P., or the GPLP, as the sole general partner of ARCH VI, may be deemed to beneficially own certain of the shares held of record by ARCH VI. The GPLP disclaims beneficial ownership of all shares held of record by ARCH VI in which the GPLP does not have an actual pecuniary interest. ARCH Venture Partners VI, LLC, or the GPLLC, as the sole general partner of the GPLP, may be deemed to beneficially own certain of the shares held of record by ARCH VI. The GPLLC disclaims beneficial ownership of all shares held of record by ARCH VI in which it does not have an actual pecuniary interest. Robert Nelsen, a member of our board of directors, is a managing director of the GPLLC and may be deemed to beneficially own certain of the shares held of record by ARCH VI. Mr. Nelsen disclaims beneficial ownership of all shares held of record by ARCH VI in which he does not have an actual pecuniary interest.

(14) Includes 95,802 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

(15) Consists of 346,974 shares held by Allegheny New Mountain Partners, L.P., 80,165 shares held by New Mountain Affiliated Investors II, L.P., 3,842,663 shares held by New Mountain Partners II (AIV-A), L.P. and 590,083 shares held by New Mountain Partners II (AIV-B), L.P. The general partner of each of the New Mountain Entities is New Mountain Investments II, L.L.C. and the manager of each of the New Mountain Entities is New Mountain Capital L.L.C. Adam Weinstein, a member of our board of directors, is a member of New Mountain Investments II, L.L.C. New Mountain Investments II, L.L.C. has decision-making power over the disposition and voting of shares of portfolio investments of each of the New Mountain Entities. New Mountain Capital, L.L.C. also has voting power over the shares of portfolio investments of the New Mountain Entities in its role as the investment advisor. New Mountain Capital, L.L.C. is a wholly-owned subsidiary of New Mountain Capital Group, L.L.C. Mr. Weinstein disclaims beneficial ownership over the shares held by the New Mountain Entities, except to the extent of his pecuniary interest therein.

(16) Includes 212,105 shares of common stock issuable upon the exercise of options exercisable within 60 days after March 16, 2015.

Securities Authorized for Issuance under Equity Compensation Plans

The following table contains information about our equity compensation plans as of December 31, 2014.

Equity Compensation Plan Information

Plan category	Number of securities to be issued upon exercise of outstanding options, warrants and rights (a)	Weighted-average exercise price of outstanding options, warrants and rights (b)	Number of securities remaining available for future issuance under equity compensation plans (excluding securities reflected in column(a)) (c)
Equity compensation plans approved by security holders	1,086,255(1)	$ 10.00	50,571(2)
Equity compensation plans not approved by security holders	—	—	—
Total	1,086,255	$ 10.00	50,571

(1) Consists of stock options outstanding as of December 31, 2014 under the 2007 Ikaria plan, 2010 Ikaria plan and 2014 equity incentive plan.

(2) Consists of shares of common stock authorized under the 2014 equity incentive plan that remained available for grant under future awards as of December 31, 2014. In January 2015, in connection with our initial public offering, our board of directors determined that we would not grant any further stock options under our 2014 equity incentive plan following the effectiveness of the registration statement for our initial public offering, which occurred in February 2015. In addition, in January 2015, our board of directors adopted, and in February 2015, our stockholders approved, our 2015 equity incentive plan, which became effective on February 13, 2015. Upon the effectiveness of the 2015 equity incentive plan, the number of shares of our common stock that were reserved for issuance under the 2015 equity incentive plan was equal to the sum of (1) 449,591 plus (2) the number of shares (up to 558,851 shares) equal to the sum of the number of shares of our common stock available for issuance under the 2014 equity incentive plan immediately prior to the effectiveness of the registration statement for our initial public offering and the number of shares of our common stock subject to outstanding awards under the 2014 equity incentive plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right plus (3) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2016 and continuing until, and including, the fiscal year ending December 31, 2025, equal to the least of (i) 798,358 shares of our common stock, (ii) a number equal to the difference between 5% of the number of shares of our common stock outstanding on the first day of the fiscal year (treating all shares of our common stock issuable upon the exercise of outstanding options and upon the conversion of outstanding shares of preferred stock, warrants or other securities convertible into shares of our common stock as outstanding for this purpose) and the number of shares of our common stock available for grant under the 2015 equity incentive plan on the first day of the fiscal year and (iii) an amount determined by our board of directors.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The following is a description of transactions since January 1, 2014 to which we have been a party, and in which any of our directors, executive officers and holders of more than 5% of our voting securities and affiliates of our directors, executive officers and holders of more than 5% of our voting securities, had or will have a direct or indirect material interest. We believe that all of the transactions described below were made on terms no less favorable to us than could have been obtained from unaffiliated third parties.

Corporate Conversion

On February 12, 2015, we completed transactions pursuant to which we converted from a Delaware limited liability company into a Delaware corporation and changed our name to Bellerophon Therapeutics, Inc. As required by the limited liability company agreement of Bellerophon Therapeutics LLC, the conversion was approved by the board of directors of Bellerophon Therapeutics LLC. In connection with the Corporate Conversion, holders of our outstanding voting units received one share of voting common stock for each voting unit held immediately prior to the Corporate Conversion, holders of our outstanding non-voting units received one share of non-voting common stock for each non-voting unit held immediately prior to the Corporate Conversion and options to purchase non-voting units became options to purchase one non-voting share of common stock for each unit underlying such options immediately prior to the Corporate Conversion, at the same aggregate exercise price in effect prior to the Corporate Conversion.

Following the Corporate Conversion and prior to our registration statement being declared effective, certain entities affiliated with certain of our principal stockholders were merged with and into us. We refer to these mergers as the Mergers. In connection with the conversion and the Mergers, these certain entities affiliated with certain of our principal stockholders received, in exchange for their equity interests in the entities being merged into us, the number of shares of our common stock that they would have held had they held our equity interests directly.

In connection with the Corporate Conversion, we entered into the following agreements:

Merger Agreement

We entered into a merger agreement with certain of our principal stockholders to effect the Mergers. Concurrently with the consummation of the conversion to a corporation, our limited liability company agreement, or the LLC agreement, was terminated (other than the provisions thereof relating to certain pre-closing tax matters and liabilities for breaches of the LLC agreement).

In the merger agreement, the companies that merged into us represented and warrantied that they did not have any liabilities, operations or businesses other than activities related to holding our common stock and other than liabilities for (i) deferred income taxes that reflect only timing differences between the treatment of items for accounting and income tax purposes and (ii) income taxes with respect to pre-closing periods which are not yet due and payable and for which we are fully indemnified. The Mergers were structured so that we did not acquire any assets (other than certain income tax receivables and an amount of cash that has been estimated in good faith to be sufficient to pay all pre-closing income taxes of the entities to be merged into us) or become responsible for any liabilities other than (i) deferred income taxes that reflect only timing differences between the treatment of items for accounting and income tax purposes and (ii) income taxes with respect to pre-closing periods which are not yet due and payable and for which we are fully indemnified. Each of our principal stockholders party to the merger agreement will indemnify us with respect to any liabilities (including tax liabilities related to pre-closing periods, other than with respect to deferred income tax liabilities that reflect only timing differences between the treatment of items for accounting and income tax purposes) of the entity related to such principal stockholder that we acquire in the merger. Any assets (other than our equity interests, certain income tax receivables and an amount of cash that has been estimated in good faith to be sufficient to pay all liabilities, including pre-closing income taxes, of the entities to be merged into us) in the entities to be merged into us were distributed to the equity holders of those entities prior to the Mergers.

Registration Rights Agreement

We have entered into a registration rights agreement with certain holders of our common stock, including our 5% stockholders and their affiliates and entities affiliated with our directors. The registration rights agreement provides these holders the right to demand that we file a registration statement or request that their shares be covered by a registration statement that we are otherwise filing. See "Description of Capital Stock—Registration Rights" for additional information regarding these registration rights.

Stockholders Agreements

New Mountain Stockholders Agreement

In February 2015, in connection with our initial public offering, we entered into a stockholders agreement with the New Mountain Entities, which provides that the New Mountain Entities are entitled to designate one director for nomination to our board of directors, to designate one director to the board of directors (or equivalent governing body) of each of our subsidiaries and to appoint the lead director of our board of directors, in each case, for so long as the New Mountain Entities or certain of their respective assignees beneficially own (i) 50% or more of the sum of (a) the number of shares of our common stock that they owned immediately prior to the closing of our initial public offering and (b) the number of shares of common stock, if any, acquired following the closing of our initial public offering (subject to in each case adjustment in the event of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification or other similar change in our capitalization) and (ii) 15% or more of our common stock outstanding (as set forth on the cover of our then most recently filed annual report on Form 10-K or quarterly report on Form 10-Q). Subject to the same ownership thresholds, the director nominated by the New Mountain Entities is entitled to serve on each committee of our board of directors and of the board of directors (or equivalent governing body) of each of our subsidiaries and the consent of the New Mountain Entities is required to establish any new committee of our board of directors or the board of directors (or equivalent governing body) of any of our subsidiaries, in each case except to the extent prohibited by applicable law or applicable listing exchange rules.

The New Mountain Entities may assign their rights to designate one director for nomination to our board of directors, to designate a director to the board of directors (or equivalent governing body) of each of our subsidiaries and to appoint the lead director of our board of directors to a person who acquires, in a transaction other than a registered public offering or a sale pursuant to Rule 144 under the Securities Act, at least 50% of the aggregate number of shares of our common stock owned, directly or indirectly, by the New Mountain Entities as of immediately prior to such transaction.

In addition, the stockholders agreement provides that, we are required to obtain the prior written approval of the New Mountain Entities to take certain actions, including, among other things, actions to:

- consolidate or merge into or with any other person, sell, lease or transfer all or a significant portion of our assets or capital stock to another person or enter into any other similar business combination transaction, or effect a liquidation;
- authorize, issue, sell, offer for sale or solicit offers to buy any shares of our common stock or any convertible securities or any other equity or debt securities or rights to acquire any of our or our subsidiaries' equity or debt securities, subject to certain exceptions, including among other things, the issuance under our stock incentive plan of grants that have been approved by our board of directors (or a board committee) and at least one director appointed by the New Mountain Entities;
- incur indebtedness or refinance any indebtedness, in each case in an amount in excess of a specified threshold;
- hire or replace our chief executive officer; or

- agree or otherwise commit to do any of the foregoing (unless the commitment is conditioned on obtaining the approval of the New Mountain Entities).

These approval rights of the New Mountain Entities will terminate when the New Mountain Entities or certain of their respective assignees beneficially own either (i) less than 50% of the sum of (a) the aggregate number of shares of our common stock that they collectively owned immediately prior to the closing of our initial public offering and (b) the number of shares of our common stock, if any, acquired following the closing of our initial public offering (subject to in each case adjustment in the event of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification or similar changes in our capitalization) or (ii) less than 15% of our common stock outstanding (as set forth on the cover of our then most recently filed annual report on Form 10-K or quarterly report on Form 10-Q). As of March 16, 2015, the New Mountain Entities held approximately 37.7% of our outstanding common stock.

Linde Stockholders Agreement

In February 2015, in connection with our initial public offering, we also entered into a stockholders agreement with Linde, which provides that Linde is entitled to designate one director for nomination to our board of directors and to designate one director to the board of directors (or equivalent governing body) of each of our subsidiaries, in each case, for so long as Linde or certain of its assignees beneficially own (i) 50% or more of the sum of (a) the number of shares of our common stock that they owned immediately prior to the closing of our initial public offering and (b) the number of shares of common stock, if any, acquired following the closing of our initial public offering (subject to in each case adjustment in the event of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification or other similar change in our capitalization) and (ii) 10% or more of our common stock outstanding (as set forth on the cover of our then most recently filed annual report on Form 10-K or quarterly report on Form 10-Q). Subject to the same ownership thresholds, the director designated by Linde is entitled to serve on each committee of our board of directors and of the board of directors (or equivalent governing body) of each of our subsidiaries and the consent of Linde is required to establish any new committee of our board of directors or the board of directors (or equivalent governing body) of any of our subsidiaries, in each case except to the extent prohibited by applicable law or applicable listing exchange rules.

Linde may assign its rights to designate one director for nomination to our board of directors and to designate a director for nomination to the board of directors (or equivalent governing body) of each of our subsidiaries to a person who acquires, in a transaction other than a registered public offering or a sale pursuant to Rule 144 under the Securities Act, at least 50% of the aggregate number of shares of our common stock owned, directly or indirectly, by Linde as of immediately prior to such transaction. As of March 16, 2015, Linde held approximately 12.6% of our outstanding common stock.

Management Rights Letters

We have entered into management rights letters with entities affiliated with certain of our principal stockholders, pursuant to which such entities are entitled to routinely consult with and advise management regarding our operations and have the right to inspect our books and records. We will also be required to deliver financial statements to such entities within 45 days after the end of each of the first three quarters of each fiscal year and 120 days after the end of each fiscal year and any other periodic reports as soon as they become available. Our management rights letter with the New Mountain Entities also provides that at any time during which the New Mountain Entities do not have the direct contractual right to designate a representative to serve on our board of directors, the New Mountain Entities will have the right to designate one observer to our board of directors. Such observer shall be entitled to attend all meetings of our board of directors and to receive copies of all materials provided to the directors, subject to customary exceptions specified in the management rights letter. Each management rights letter will terminate on the date the entity party thereto (or principal stockholder with which such entity is affiliated) no longer holds any of our securities.

Indemnification Agreements

Our certificate of incorporation provides that we will indemnify our directors and officers to the fullest extent permitted by Delaware law. In addition, we have entered into indemnification agreements with each of our directors and officers. See "Executive Compensation—Limitations on Liability and Indemnification" for additional information regarding these agreements.

Relationship with Ikaria

Prior to the Spin-Out on February 12, 2014, we were a wholly-owned subsidiary of Ikaria. See "Business—Relationship with Ikaria after the Spin-Out." Following the Spin-Out, Ikaria ceased to hold any of our equity interests and we became a stand-alone company. On March 5, 2015, Mallinckrodt and Ikaria announced that they had entered into a definitive agreement under which a subsidiary of Mallinckrodt will acquire Ikaria. Mallinckrodt and Ikaria have announced that they expect this transaction to be completed in the second calendar quarter of 2015.

Separation and Distribution Agreement

In connection with the Spin-Out, we and Ikaria entered into a separation and distribution agreement which sets forth the key provisions relating to the separation of our business from Ikaria's other businesses. The separation and distribution agreement described the assets and liabilities that remained with or were transferred to us and those that remained with or were transferred to Ikaria and the terms of Ikaria's distribution of all of our then outstanding units to its stockholders. The separation and distribution agreement provides for a full and complete release and discharge of all liabilities between Ikaria and us, except as set forth in the agreement. We and Ikaria each agreed to indemnify, defend and hold harmless the other party and its subsidiaries, and each of their respective past and present directors, officers and employees, and each of their respective permitted successors and assigns, from any and all damages relating to, arising out of or resulting from, among other things, our business and certain additional specified liabilities or Ikaria's business and certain additional specified liabilities, as applicable. The separation and distribution agreement also provides that we and Ikaria will each use reasonable best efforts, including by cooperating with the other party, to, among other things, effect the transfer of any assets being transferred in connection with the Spin-Out that had not been transferred as of the date of the Spin-Out.

In connection with the Spin-Out, we and Ikaria have entered into other agreements that will govern various interim and ongoing relationships between us and Ikaria. These agreements, the material terms of which are summarized below, include:

- transition services agreements;
- an exclusive cross-license, technology transfer, and regulatory matters agreement;
- an employee matters agreement;
- agreements not to compete; and
- drug and device supply agreements.

The principal agreements described below are filed as exhibits to this Annual Report on Form 10-K, and the summaries of each of these agreements below set forth the terms of the agreements that we believe are material. These summaries are qualified in their entireties by reference to the full text of the applicable agreements, which are incorporated by reference into this Annual Report on Form 10-K.

Services Agreements

Transition Services Agreement. In February 2014, we entered into the TSA. Pursuant to the terms and conditions of the TSA, Ikaria has agreed to use commercially reasonable efforts to provide certain services to us, including human resources support, real estate support, information technology support, accounting and tax support, treasury support, financial planning and analysis support, purchasing support, management/executive services, legal services, quality services, regulatory services, drug and device safety services, business development support, biometrics support and manufacturing support. Ikaria is obligated, subject to the terms of the TSA (including the early termination provisions thereof and our obligation to use commercially reasonable efforts to provide the services for ourselves as soon as practicable), to provide such services until February 2016.

Ikaria has also agreed, on the terms and subject to the conditions of the TSA, to use commercially reasonable efforts to allow our employees to remain in Ikaria's Hampton, New Jersey facility for the continued operation of our business during the term of the TSA.

We are obligated to pay Ikaria a service fee in the amount of $772,000 per month and to reimburse Ikaria for any out-of-pocket expenses incurred in connection with its provisions of services under the TSA, any taxes imposed on Ikaria in connection with the performance or delivery of services under the TSA and any costs and expenses incurred by Ikaria in connection with the performance of any services that require resources outside of the existing resources of Ikaria or that otherwise interfere with the ordinary operations of Ikaria's business. This monthly service fee is payable by us regardless of the frequency or quantity of services actually utilized by us under the TSA, and our obligation to pay such monthly service fee for 24 months will survive any early termination of the TSA. We are also obligated to pay any fees, costs, expenses or other amounts incurred by Ikaria to obtain the right to allow our employees to remain in the Hampton, New Jersey facility during the term of the TSA. At the time of the Spin-Out, we deposited the sum of $18.5 million into escrow, representing the aggregate of the $772,000 monthly service fees payable by us under the TSA, to guarantee payment of the monthly service fees by us.

2015 Services Agreement. We entered into a services agreement with Ikaria, effective as of January 1, 2015, which we refer to as the 2015 Services Agreement. Pursuant to the terms of the 2015 Services Agreement, we have agreed to use commercially reasonable efforts to provide certain services to Ikaria, including services related to regulatory matters, drug and device safety, clinical operations, biometrics and scientific affairs. We are obligated, subject to the terms of the 2015 Services Agreement, to provide such services until February 2016. In connection with the execution of the 2015 Services Agreement, Ikaria paid us a one-time service fee in the amount of $916,666 and is obligated to pay us a service fee in the amount of $83,333 per month, subject to our obligation to perform the services.

In addition, pursuant to the terms and conditions of the 2015 Services Agreement, Ikaria has agreed to use commercially reasonable efforts to provide certain services to us, including services related to information technology, and servicing and upgrades of INOpulse devices. Ikaria is obligated, subject to the terms of the 2015 Services Agreement, to provide such services until February 2016. We are obligated to pay Ikaria certain fees under the 2015 Services Agreement that total, in the aggregate, approximately $215,000, subject to termination of the 2015 Services Agreement.

Exclusive Cross-License, Technology Transfer and Regulatory Matters Agreement

In February 2014, we entered into an exclusive cross-license, technology transfer and regulatory matters agreement with Ikaria. Pursuant to the terms of the license agreement, Ikaria granted to us a fully paid-up, non-royalty bearing, exclusive license under specified intellectual property rights controlled by Ikaria to engage in the development, manufacture and commercialization of nitric oxide, devices to deliver nitric oxide and related services for or in connection with out-patient, chronic treatment of patients with PAH, PH-COPD or PH-IPF, which we refer to collectively as the Bellerophon indications.

We have granted to Ikaria a fully paid-up, non-royalty-bearing, exclusive license under specified intellectual property rights that we control to engage in the development, manufacture and commercialization of products and services for or used in connection with the diagnosis, prevention or treatment, whether in- or out-patient, of certain conditions and diseases other than the Bellerophon indications and for the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital, which we refer to collectively as the Ikaria nitric oxide business.

We have agreed that, during the term of the license agreement, we will not, without the prior written consent of Ikaria, grant a sublicense under any of the intellectual property licensed to us under the license agreement to any of our affiliates or any third party, in either case, that directly or indirectly competes with the Ikaria nitric oxide business. We have also agreed that we will include certain restrictions in our agreements with customers of our products to ensure that such products will only be used for the Bellerophon indications.

The license agreement will expire on a product-by-product basis for products for a specific Bellerophon indication at such time as we are no longer developing or commercializing any product for such indication. The license agreement may be terminated by either party in the event an act or order of a court or governmental authority prohibits either party from substantially performing under the license agreement. Either party may also terminate the license agreement in the event of an uncured material breach by the other party or in the event the other party is insolvent or in bankruptcy proceedings. Ikaria may also terminate the license agreement if we or any of our affiliates breach the agreements not to compete described below, or if we or any successor to our rights under the license agreement markets a generic nitric oxide product that is competitive with INOmax. Under certain circumstances, if the license agreement is terminated, the licenses granted to Ikaria by us will survive such termination.

Employee Matters Agreement

In February 2014, we entered into an employee matters agreement with Ikaria, pursuant to which the employment of certain Ikaria employees was transferred to us or our subsidiaries on the terms and conditions set forth therein. The employee matters agreement also sets forth the treatment of outstanding Ikaria stock options and RSUs in connection with the Spin-Out. We have agreed to assume and pay, perform, fulfill and discharge, in accordance with the terms of the employee matters agreement, all liabilities to or relating to such transferred employees. Effective as of the date of the Spin-Out, such transferred employees terminated participation in Ikaria's employee benefit plans, and we or our subsidiaries adopted employee benefit plans substantially similar to the following Ikaria plans: a 401(k) plan, a medical and dental plan, long-term disability, short-term disability, life and accidental death and dismemberment and flexible spending accounts, pursuant to the terms of the employee matters agreement.

Agreements Not to Compete

In September 2013, October 2013 and February 2014, we and each of our subsidiaries entered into an agreement not to compete with a subsidiary of Ikaria, which we refer to collectively as the agreements not to compete. Pursuant to the agreements not to compete, we and each of our subsidiaries agreed not to engage, anywhere in the world, in any manner, directly or indirectly, until the earlier of five years after the effective date of such agreement not to compete or the date on which Ikaria and all of its subsidiaries are no longer engaged in such business, in:

- the development, manufacture, commercialization, promotion, sale, import, export, servicing, repair, training, storage, distribution, transportation, licensing or other handling or disposition of any product or service (including, without limitation, any product or service that utilizes, contains or includes nitric oxide for inhalation, a device intended to deliver nitric oxide or a service that delivers or supports the delivery of nitric oxide), bundled or unbundled, for or used in connection with (a) the diagnosis, prevention or treatment, in both adult and/or pediatric populations, and whether in- or out-patient, of: (i) hypoxic respiratory failure associated with pulmonary hypertension,

(ii) pulmonary hypertensive episodes and right heart failure associated with cardiovascular surgery, (iii) bronchopulmonary dysplasia, (iv) the management of ventilation-perfusion mismatch in acute lung injury, (v) the management of ventilation-perfusion mismatch in acute respiratory distress syndrome, (vi) the management of pulmonary hypertension episodes and right heart failure in congestive heart failure, (vii) pulmonary edema from high altitude sickness, (viii) the management of pulmonary hypertension episodes and right heart failure in pulmonary or cardiac surgery, (ix) the management of pulmonary hypertension episodes and right heart failure in organ transplant, (x) sickle cell vaso-occlusive crisis, (xi) hypoxia associated with pneumonia or (xii) ischemia-reperfusion injury or (b) the use of nitric oxide to treat or prevent conditions that are primarily managed in the hospital; or

- any and all development, manufacture, commercialization, promotion, sale, import, export, storage, distribution, transportation, licensing, or other handling or disposition of any terlipressin or any other product within the pressin family, (a) intended to treat (i) hepatorenal syndrome in any form, (ii) bleeding esophageal varices or (iii) septic shock or (b) for or in connection with the management of low blood pressure.

The agreements not to compete expressly exclude the Bellerophon indications.

Supply Agreements

Device Clinical Supply Agreement. In February 2014, we entered into the device supply agreement, pursuant to which Ikaria will use commercially reasonable efforts to manufacture and supply our requirements for certain nitric oxide delivery devices specified in the device supply agreement for use in our clinical programs for PAH and PH-COPD. Pursuant to the device supply agreement, we will pay to Ikaria an amount equal to Ikaria's internal and external manufacturing cost plus 20%. The device supply agreement expired on February 9, 2015.

Drug Clinical Supply Agreement. In February 2014, we entered into the drug supply agreement, pursuant to which Ikaria has agreed to use commercially reasonable efforts to manufacture and supply, and we have agreed to acquire from Ikaria, our requirements for nitric oxide for inhalation and corresponding placebo for use in our clinical programs for PAH, PH-COPD and PH-IPF. Pursuant to the drug supply agreement, we will pay to Ikaria an amount equal to Ikaria's internal and external manufacturing cost plus 20%. Under the terms of the drug supply agreement, we have also granted Ikaria a right of first negotiation in the event that we desire to obtain supply of nitric oxide for inhalation and corresponding placebo (or any variant thereof or any version with different specifications) for commercial use. The drug supply agreement will expire on a product-by-product basis on the date we discontinue clinical development of such product. In addition, either party may terminate the drug supply agreement in the event of an uncured material breach by the other party.

Directors and Officers of Ikaria

Daniel Tassé, a member of our board of directors, currently serves as President and Chief Executive Officer and is a member of the board of directors of Ikaria. Matthew Holt, a member of our board of directors, is a member of the board of directors of Ikaria.

Participation in Initial Public Offering

In our initial public offering, certain of our directors, executive officers and 5% stockholders and their affiliates purchased an aggregate of 1,914,464 shares of our common stock. Each of those purchases was made through the underwriters or through the directed share program at the initial public offering price of $12.00 per share. The following table sets forth the aggregate number of shares of our common stock that these directors, executive officers and 5% stockholders and their affiliates purchased in our initial public offering:

Purchaser(1)	Shares of common stock	Total purchase price
New Mountain Entities	1,070,166	$ 12,841,992
Linde	358,916	$ 4,306,992
ARCH	212,666	$ 2,551,992
Venrock	211,916	$ 2,542,992
Jonathan M. Peacock	20,800	$ 249,600
Manesh Naidu	1,500	$ 18,000
Reinilde Heyrman	1,500	$ 18,000
Martin Meglasson	12,000	$ 144,000
Daniel Tassé	25,000	$ 300,000

(1) See "Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters" for more information about the shares held by the below identified entities, directors and executive officers.

Policies and Procedures for Related Person Transactions

Our board of directors has adopted written policies and procedures for the review of any transaction, arrangement or relationship in which we were or are to be a participant, the amount involved exceeds $120,000 and one of our executive officers, directors, director nominees or 5% stockholders, or their immediate family members, each of whom we refer to as a "related person," has a direct or indirect material interest.

If a related person proposes to enter into such a transaction, arrangement or relationship, which we refer to as a "related person transaction," the related person must report the proposed related person transaction to our General Counsel or Chief Financial Officer, or in each case an individual performing similar functions. The policy calls for the proposed related person transaction to be reviewed and, if deemed appropriate, approved by our audit committee. Whenever practicable, the reporting, review and approval will occur prior to entry into the transaction. If advance review and approval is not practicable, the audit committee will review, and, in its discretion, may ratify the related person transaction. The policy also permits the chairman of the audit committee to review and, if deemed appropriate, approve proposed related person transactions that arise between committee meetings, subject to ratification by the committee at its next meeting. Any related person transactions that are ongoing in nature will be reviewed annually.

A related person transaction reviewed under the policy will be considered approved or ratified if it is authorized by the audit committee after full disclosure of the related person's interest in the transaction. As appropriate for the circumstances, the committee will review and consider:

- the related person's interest in the related person transaction;
- the approximate dollar value of the amount involved in the related person transaction;
- the approximate dollar value of the amount of the related person's interest in the transaction without regard to the amount of any profit or loss;
- whether the transaction was undertaken in the ordinary course of our business;
- whether the terms of the transaction are no less favorable to us than terms that could have been reached with an unrelated third party;

- the purpose of, and the potential benefits to us of, the transaction; and

- any other information regarding the related person transaction or the related person in the context of the proposed transaction that would be material to investors in light of the circumstances of the particular transaction.

The audit committee may approve or ratify the transaction only if the committee determines that, under all of the circumstances, the transaction is in our best interests. The committee may impose any conditions on the related person transaction that it deems appropriate.

In addition to the transactions that are excluded by the instructions to the SEC's related person transaction disclosure rule, our board of directors has determined that the following transactions do not create a material direct or indirect interest on behalf of related persons and, therefore, are not related person transactions for purposes of this policy:

- interests arising solely from the related person's position as an executive officer of another entity (whether or not the person is also a director of such entity) that is a participant in the transaction, where (a) the related person and all other related persons own in the aggregate less than a 10% equity interest in such entity, (b) the related person and his or her immediate family members are not involved in the negotiation of the terms of the transaction and do not receive any special benefits as a result of the transaction and (c) the amount involved in the transaction is less than the greater of $200,000 or 5% of the annual gross revenues of the company receiving payment under the transaction; and

- a transaction that is specifically contemplated by provisions of our charter or bylaws.

The policy provides that transactions involving compensation of executive officers shall be reviewed and approved by the compensation committee in the manner specified in its charter.

We did not have a written policy regarding the review and approval of related person transactions prior to our initial public offering. Nevertheless, with respect to such transactions, it was our policy for our board of directors to consider the nature of and business reason for such transactions, how the terms of such transactions compared to those which might be obtained from unaffiliated third parties and whether such transactions were otherwise fair to and in the best interests of, or not contrary to, our best interests. In addition, all related person transactions required prior approval, or later ratification, by our board of directors.

Director Independence

NASDAQ rules require that a majority of our board of directors be independent within one year of listing, which in our case was February 13, 2015. In addition, the NASDAQ rules require that, subject to specified exceptions, each member of a listed company's audit, compensation and nominating and corporate governance committees be independent and that audit committee members also satisfy independence criteria set forth in Rule 10A-3 under the Exchange Act. Under NASDAQ rules, a director will only qualify as an "independent director" if, in the opinion of our board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director. In order to be considered independent for purposes of Rule 10A-3, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors or any other board committee, accept, directly or indirectly, any consulting, advisory or other compensatory fee from the listed company or any of its subsidiaries or otherwise be an affiliated person of the listed company or any of its subsidiaries. Our board of directors has determined that Messrs. Holt, Luehring, Moura, Nelsen and Weinstein are "independent directors," as defined under Rule 5605(a)(2) of the NASDAQ rules. In making such determination, our board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances that our board of directors deemed relevant in

determining their independence, including the beneficial ownership of our capital stock by each non-employee director.

The phase-in periods with respect to director independence under the applicable NASDAQ rules allow us to have only one independent member on each of the audit committee, compensation committee and nominating and corporate governance committee upon the listing date of our common stock, a majority of independent members on each of these committees within 90 days of the listing date and fully independent committees within one year of the listing date.

Our board of directors has determined that Mr. Luehring, who is a member of our audit committee, Messrs. Holt and Nelsen, who are members of our compensation committee, and Messrs. Holt and Moura, who are members of our nominating and corporate governance committee, satisfy the independence standards for their respective committees established by the SEC and NASDAQ rules, as applicable, including, in the case of the audit committee member, the independence requirements of Rule 10A-3 under the Exchange Act and, in the case of the compensation committee members, the independence requirements under Rule 10C-1 under the Exchange Act. In making such determinations, our board of directors considered the relationships that each such non-employee director has with our company and all other facts and circumstances that our board of directors deemed relevant in determining independence, including the beneficial ownership of our capital stock by each non-employee director. Our board of directors has determined that neither Mr. Moura, who is a member of our audit committee, nor Mr. Weinstein, who is the chair of our audit committee, is currently independent under Rule 10A-3 of the Exchange Act, but determined that Mr. Moura will be permitted to remain on the audit committee for a period of up to 90 days following the listing date and Mr. Weinstein will be permitted to remain on the audit committee for a period of up to one year following the listing date, in each case in accordance with the phase-in period under NASDAQ rules.

Item 14. Principal Accountant Fees and Services

Auditors' Fees

The following table summarizes the fees of KPMG LLP, our registered independent public accounting firm, billed to us for each of the last two fiscal years.

Fee Category	2014	2013
Audit Fees(1)	$ 843,806	$ 138,000
Audit-Related Fees	—	—
Tax Fees	—	—
All Other Fees	—	—
Total Fees	$ 843,806	$ 138,000

(1) Audit fees consist of fees for the audit of our financial statements and the review of our interim financial statements and services associated with our registration statement on Form S-1.

Pre-Approval Policies and Procedures

The audit committee of our board of directors has adopted policies and procedures for the pre-approval of audit and non-audit services for the purpose of maintaining the independence of our independent auditor. We

may not engage our independent auditor to render any audit or non-audit service unless either the service is approved in advance by the audit committee, or the engagement to render the service is entered into pursuant to the audit committee's pre-approval policies and procedures. Notwithstanding the foregoing, pre-approval is not required with respect to the provision of services, other than audit, review or attest services, by the independent auditor if the aggregate amount of all such services is no more than 5% of the total amount paid by us to the independent auditor during the fiscal year in which the services are provided, such services were not recognized by us at the time of the engagement to be non-audit services and such services are promptly brought to the attention of the audit committee and approved prior to completion of the audit by the audit committee.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(1) Financial Statements

Our consolidated financial statements are set forth in Part II, Item 8 of this Annual Report on Form 10-K and are incorporated herein by reference.

(2) Financial Statement Schedules

No financial statement schedules have been filed as part of this Annual Report on Form 10-K because they are not applicable or are not required or because the information is otherwise included herein.

(3) Exhibits

The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following our financial statements. The Exhibit Index is incorporated herein by reference.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: March 31, 2015

BELLEROPHON THERAPEUTICS, INC.

By: /s/ Jonathan M. Peacock
Jonathan M. Peacock
Chairman, President and Chief Executive Officer
(Principal Executive Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Jonathan M. Peacock Jonathan M. Peacock	Chairman, President and Chief Executive Officer (Principal Executive Officer)	March 31, 2015
/s/ David Abrams David Abrams	Treasurer (Principal Financial and Accounting Officer)	March 31, 2015
/s/ Matthew Holt Matthew Holt	Director	March 31, 2015
/s/ Jens Luehring Jens Luehring	Director	March 31, 2015
/s/ Andre V. Moura Andre V. Moura	Director	March 31, 2015
/s/ Robert T. Nelsen Robert T. Nelsen	Director	March 31, 2015
/s/ Daniel Tassé Daniel Tassé	Director	March 31, 2015
/s/ Adam Weinstein Adam Weinstein	Director	March 31, 2015

EXHIBIT INDEX

Exhibit Number	Description of Exhibit
2.1*	Plan of Conversion
2.2*	Agreement and Plan of Merger
3.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on February 25, 2015)
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-36845) filed with the SEC on February 25, 2015)
4.1	Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1/A (File No. 333-201474) filed with the SEC on February 3, 2015)
4.2	Stockholders Agreement, dated February 12, 2015, between the Registrant and Linde North America, Inc.
4.3	Stockholders Agreement, dated February 12, 2015, among the Registrant and New Mountain Partners II (AIV-A), L.P., New Mountain Partners II (AIV-B), L.P., New Mountain Affiliated Investors II, L.P. and Allegheny New Mountain Partners, L.P.
10.1+	Assumed 2007 Ikaria Stock Option Plan (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.2+	Assumed 2010 Ikaria Long Term Incentive Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.3+	2014 Equity Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.4+	Form of Option Agreement under 2014 Equity Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.5+	2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on February 3, 2015)
10.6+	Form of Incentive Stock Option Agreement under 2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on February 3, 2015)
10.7+	Form of Nonstatutory Stock Option Agreement under 2015 Equity Incentive Plan (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on February 3, 2015)
10.8†	Amended and Restated License and Commercialization Agreement, dated as of August 26, 2009, among Ikaria Development Subsidiary One LLC, BioLineRx Ltd. and BioLine Innovations Jerusalem L.P., as amended
10.9	Form of Agreement Not to Compete, entered into by Ikaria Acquisition LLC and each of the Registrant, Bellerophon BCM LLC, Bellerophon Pulse Technologies LLC and Bellerophon Services, Inc. (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.10†	Separation and Distribution Agreement, dated as of February 9, 2014, among the Registrant, Ikaria, Inc. and Ikaria Acquisition LLC (incorporated by reference to Exhibit 10.10 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)

10.11†	Services Agreement, effective as of January 1, 2015, between the Registrant and Ikaria, Inc. (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on February 3, 2015)
10.12†	Drug Clinical Supply Agreement, dated as of February 9, 2014, between Bellerophon Pulse Technologies LLC and INO Therapeutics LLC (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.13†	Employee Matters Agreement, dated as of February 9, 2014, between the Registrant and Ikaria, Inc. (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.14†	Exclusive Cross-License, Technology Transfer and Regulatory Matters Agreement, dated February 9, 2014, between Bellerophon Pulse Technologies LLC and INO Therapeutics LLC, as amended on March 27, 2014 (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.15†	Transition Services Agreement, dated as of February 9, 2014, between the Registrant and Ikaria, Inc. (incorporated by reference to Exhibit 10.15 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.16	Registration Rights Agreement, dated February 12, 2015, among the Registrant, New Mountain Partners II (AIV-A), L.P., New Mountain Partners II (AIV-B), L.P., Allegheny New Mountain Partners, L.P., New Mountain Affiliated Investors II, L.P., ARCH Venture Fund VI, L.P., Venrock Partners, L.P., Venrock Associates IV, L.P., Venrock Entrepreneurs Fund IV, L.P., Linde North America, Inc., 5AM Ventures LLC and Aravis Venture I L.P.
10.17	Form of Indemnification Agreement between the Registrant and each of its executive officers and directors (incorporated by reference to Exhibit 10.17 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.18+	Assumed Employment Agreement, dated January 4, 2012, between Manesh Naidu and Ikaria, Inc. (incorporated by reference to Exhibit 10.18 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.19+	Assumed Employment Agreement, dated August 10, 2010, between Martin Meglasson and Ikaria, Inc. (incorporated by reference to Exhibit 10.19 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.20+	Assumed Employment Agreement, dated March 26, 2012, between Reinilde Heyrman and Ikaria, Inc. (incorporated by reference to Exhibit 10.20 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.21+	Form of Retention Bonus Letter for Executive Officers (incorporated by reference to Exhibit 10.21 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.22+	Employment Agreement, dated June 20, 2014, between Jonathan M. Peacock, the Registrant and Bellerophon Services, Inc. (incorporated by reference to Exhibit 10.22 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
10.23	Form of Management Rights Letter between the Registrant and certain of its stockholders (incorporated by reference to Exhibit 10.23 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-201474) filed with the SEC on January 13, 2015)
23.1	Consent of KPMG LLP independent registered public accounting firm
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended

32.1 Certification of Principal Executive Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

32.2 Certification of Principal Financial Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

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* Schedules and exhibits have been omitted pursuant to Item 601(b)(2) of Regulation S-K. The Registrant hereby undertakes to furnish copies of any of the omitted schedules and exhibits upon request by the Securities and Exchange Commission.

† Confidential treatment has been granted as to certain portions, which portions have been omitted and separately filed with the Securities and Exchange Commission.

+ Management contract or compensatory plan or arrangement filed in response to Item 15(a)(3) of the Instructions to the Annual Report on Form 10-K.

Exhibit 2.1

PLAN OF CONVERSION
Converting
Bellerophon Therapeutics LLC
(a Delaware limited liability company)
into
Bellerophon Therapeutics, Inc.
(a Delaware corporation)

THIS PLAN OF CONVERSION (this "***Plan***"), dated as of February 12, 2015, is hereby adopted and approved by Bellerophon Therapeutics LLC, a limited liability company formed under the laws of Delaware (the "***LLC***"), to set forth the terms, conditions and procedures governing the conversion of the LLC to a Delaware corporation pursuant to Section 18-216 of the Delaware Limited Liability Company Act (the "***DLLCA***") and Section 265 of the Delaware General Corporation Law (the "***DGCL***").

WHEREAS, the LLC is a limited liability company formed and existing under the laws of the State of Delaware and is operating under the Amended and Restated Limited Liability Company Agreement of the LLC, dated as of February 9, 2014, as amended (the "***LLC Agreement***"), by and among the LLC and the Members (as defined in the LLC Agreement);

WHEREAS, the Board (as defined in the LLC Agreement) has determined that it is in the best interests of the LLC for the LLC to convert to a Delaware corporation pursuant to Section 18-216 of the DLLCA and Section 265 of the DGCL upon the terms and conditions and in accordance with the procedures set forth herein, and the Board has authorized and approved the Conversion (as defined below) and the execution, delivery and filing of any and all instruments, certificates and documents necessary or desirable in connection therewith;

WHEREAS, pursuant to Section 14.01 of the LLC Agreement, the Board has the right to cause the LLC to convert to a corporation in accordance with the terms of the LLC Agreement by such means as the Board shall select;

WHEREAS, pursuant to the terms of a Merger Agreement, dated as of the date hereof (the "***Merger Agreement***"), following the Conversion each of New Mountain Partners II Special (AIV-A), L.P., IRDO Holding Corp., Venrock IK Holdings BT, Inc. and 5AM-BT, Inc. shall merge with and into the Corporation (as defined below), and the Corporation shall be the surviving entity in such mergers; and

WHEREAS, it is intended that the Conversion (as defined below) and each of the mergers undertaken pursuant to the Merger Agreement together constitute an integrated transaction governed by Section 351 of the Internal Revenue Code of 1986, as amended.

NOW, THEREFORE, the LLC does hereby adopt this Plan to effectuate the conversion of the LLC to a Delaware corporation as follows:

1. Conversion; Effect of Conversion. Upon and subject to the terms and conditions of this Plan and pursuant to the relevant provisions of the DLLCA and the DGCL, including without limitation Section 18-216 of the DLLCA and Section 265 of the DGCL, the LLC shall convert (the "***Conversion***") to a Delaware corporation named "Bellerophon Therapeutics, Inc." (the "***Corporation***") at the Effective Time (as defined below). The Corporation shall thereafter be subject to all of the provisions of the DGCL, except that notwithstanding Section 106 of the DGCL, the existence of the Corporation shall be deemed to have commenced on the date the LLC commenced its existence. The Conversion shall not affect any obligations or liabilities of the LLC incurred prior to the Effective Time. The LLC shall not be required to wind up its affairs or pay its liabilities and distribute its assets, and the Conversion shall not constitute a dissolution of the LLC and shall constitute a continuation of the existence of the LLC in the form of a Delaware corporation. Upon the Effective Time, all of the rights, privileges and powers of the LLC, and all property and all debts due to the LLC, as well as all other things and causes of action belonging to the LLC, shall remain vested in the Corporation and shall be the property of the Corporation, and the title to any real property vested by deed or otherwise in the LLC shall not revert or be in any way impaired by reason of the Conversion, and all rights of creditors and all liens upon any property of the LLC shall be preserved unimpaired, and all debts, liabilities and duties of the LLC shall remain attached to the Corporation and may be enforced against it to the same extent as if such debts, liabilities and duties had been incurred or contracted by it in its capacity as a corporation.

2. Certificate of Conversion; Certificate of Incorporation; Effective Time. The Conversion shall be effected by the filing with the Secretary of State of the State of Delaware of: (a) a duly executed Certificate of Conversion, substantially in the form of Exhibit A attached hereto (the "***Certificate of Conversion***"), and (b) a duly executed Certificate of Incorporation of the Corporation, in the form of Exhibit B attached hereto (the "***Certificate of Incorporation***"). The Conversion shall be effective immediately upon the filing of (i) the Certificate of Conversion and (ii) the Certificate of Incorporation with the Secretary of State of the State of Delaware or at such later time as may be specified in both the Certificate of Conversion and the Certificate of Incorporation (such time of effectiveness, the "***Effective Time***").

3. Bylaws of the Corporation. As promptly as practical following the Effective Time, the board of directors of the Corporation shall adopt the Bylaws of the Corporation in substantially the form of Exhibit C attached hereto (the "***Bylaws***"). From and after the Effective Time, except as set forth in Section 7 below, the LLC Agreement shall terminate and no longer govern the affairs of the Corporation, but instead the affairs of the Corporation shall be governed by the DGCL, the Certificate of Incorporation and, following their adoption by the board of directors of the Corporation, the Bylaws.

4. Directors and Officers. At the Effective Time, (a) the members of the Board of the LLC as of the Effective Time shall be the members of the board of directors of the Corporation and shall hold office until their respective successors are duly elected and qualified, or their earlier death, resignation or removal and (b) the officers of the LLC as of the Effective Time shall be the officers of the Corporation and shall hold office until their respective successors are duly elected and qualified, or their earlier death, resignation or removal. The LLC and, after the Effective Time, the Corporation and its board of directors shall take all necessary actions to

cause each of such individuals to be appointed as a director and/or officer, as the case may be, of the Corporation.

5. Effect of the Conversion on Equity Interests in the LLC.

(a) Conversion of Outstanding Securities. Subject to the terms and conditions of this Plan, at the Effective Time, automatically by virtue of the Conversion and without any further action on the part of the LLC, the Corporation or any holder of Units (as defined in the LLC Agreement) or options to purchase Units:

(i) each Voting Unit (as defined in the LLC Agreement) of the LLC that is outstanding immediately prior to the Effective Time shall be converted into one share of voting common stock, par value $0.01 per share, of the Corporation ("***Voting Common Stock***"), and as of the Effective Time each such share of Voting Common Stock shall be duly and validly issued, fully paid and nonassessable;

(ii) each Non-Voting Unit (as defined in the LLC Agreement) of the LLC that is outstanding immediately prior to the Effective Time shall be converted into one share of non-voting common stock, par value $0.01 per share, of the Corporation ("***Non-Voting Common Stock***" and, together with the Voting Common Stock, the "***Common Stock***"), and as of the Effective Time each such share of Non-Voting Common Stock shall be duly and validly issued, fully paid and nonassessable; and

(iii) each option to purchase a Non-Voting Unit (each, an "***LLC Option***") that is outstanding immediately prior to the Effective Time shall be converted into an option to purchase, upon the same terms and conditions (including, but not limited to, the exercise price), the same number of shares of Non-Voting Common Stock (each, a "***Corporation Option***") as the number of Non-Voting Units that were subject to the LLC Option immediately prior to the Conversion.

(b) No Further Ownership Rights in Units. All shares of Voting Common Stock and Non-Voting Common Stock into which Units are converted pursuant to the Conversion in accordance with the terms of this Section 5 shall be deemed to have been issued in full satisfaction of all rights pertaining to such Units. Immediately following the Effective Time, Units shall cease to exist, and the holder of any Units immediately prior to the Effective Time shall cease to have any rights with respect thereto.

(c) No Further Ownership Rights in LLC Options. All Corporation Options into which LLC Options are converted in accordance with the terms of this Section 5 shall be deemed to have been issued in full satisfaction of all rights pertaining to such LLC Options. Immediately following the Effective Time, LLC Options shall cease to exist, and the holder of any LLC Options immediately prior to the Effective Time shall cease to have any rights with respect thereto.

(d) No Impact on Vesting Restrictions and Repurchase Rights. The conversion of Units and LLC Options pursuant to Section 5(a) will not limit, impair or otherwise modify any vesting restrictions or repurchase rights with respect to any equity issued by the LLC

to any officer or employee of the LLC or any other person, which vesting restrictions and repurchase rights shall continue to apply to the shares of Common Stock or Corporation Options, as applicable, issued hereby to any such persons until the expiration of such vesting restrictions and repurchase rights in accordance with their terms. The Corporation Options shall remain governed by the terms and conditions of the applicable option plan of the Corporation.

(e) Transfer Books. At the Effective Time, there shall be no further registration of transfers on the transfer books of the LLC of any Units that were outstanding immediately prior to the Effective Time.

(f) Registration in Book-Entry. Shares of Common Stock issued in connection with the Conversion shall be uncertificated, and the Corporation shall register, or cause to be registered, such shares into which each outstanding Unit shall have been converted as a result of the Conversion in book-entry form.

6. Licenses, Permits, Titled Property, Etc. As applicable, following the Effective Time, to the extent required, the Corporation shall apply for new state tax identification numbers, qualifications to conduct business (including as a foreign corporation), licenses, permits and similar authorizations on its behalf and in its own name in connection with the Conversion and to reflect the fact that it is a corporation. As required or appropriate, following the Effective Time, all real, personal and intangible property of the LLC which was titled or registered in the name of the LLC shall be re-titled or re-registered, as applicable, in the name of the Corporation by appropriate filings and/or notices to the appropriate parties (including, without limitation, any applicable governmental agencies). In addition, following the Effective Time, the LLC's customer, vendor and other communications (e.g., business cards, letterhead, websites, etc.) shall be revised to reflect the Conversion and the Corporation's corporate status.

7. Termination of LLC Agreement. As of the Effective Time, the LLC Agreement shall be terminated and of no further force and effect. Notwithstanding the foregoing, the termination of the LLC Agreement shall not relieve any party thereto from any liability arising in connection with any breach by such party of the LLC Agreement, arising prior to the Effective Time.

8. Further Assurances. If, at any time after the Effective Time, the Corporation shall determine or be advised that any deeds, bills of sale, assignments, agreements, documents or assurances or any other acts or things are necessary, desirable or proper, consistent with the terms of this Plan, (a) to vest, perfect or confirm, of record or otherwise, in the Corporation its right, title or interest in, to or under any of the rights, privileges, immunities, powers, purposes, franchises, properties or assets of the LLC, or (b) to otherwise carry out the purposes of this Plan, the Corporation and its proper officers and directors (or their designees) are hereby authorized to solicit in the name of the LLC any third party consents or other documents required to be delivered by any third party, to execute and deliver, in the name and on behalf of the LLC, all such deeds, bills of sale, assignments, agreements, documents and assurances and do, in the name and on behalf of the LLC, all such other acts and things necessary, desirable or proper to vest, perfect or confirm its right, title or interest in, to or under any of the rights, privileges, immunities, powers, purposes, franchises, properties or assets of the LLC and otherwise to carry out the purposes of this Plan.

9. Implementation and Interpretation; Termination and Amendment. This Plan shall be implemented and interpreted, prior to the Effective Time, by the Board and, following the Effective Time, by the board of directors of the Corporation, (a) each of which shall have full power and authority to delegate and assign any matters covered hereunder to any other party(ies), including, without limitation, any officers of the LLC or any officers of the Corporation, as the case may be, and (b) the interpretations and decisions of which shall be final, binding, and conclusive on all parties. The Board at any time prior to the Effective Time may terminate, amend or modify this Plan. Upon such termination of this Plan, if the Certificate of Conversion and the Certificate of Incorporation have been filed with the Secretary of State of the State of Delaware, but have not become effective, any person or entity that was authorized to execute, deliver and file such certificates may execute, deliver and file a Certificate of Termination of such certificates.

10. Third Party Beneficiaries. This Plan shall not confer any rights or remedies upon any person or entity other than as express provided herein.

11. Severability. Whenever possible, each provision of this Plan will be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Plan is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of this Plan.

12. Governing Law. This Plan shall be governed by and construed in accordance with the laws of the State of Delaware, without regard to the conflicts of laws rules of such state.

[*Remainder of page intentionally left blank.*]

IN WITNESS WHEREOF, the LLC has caused this Plan to be executed by its duly authorized representative as of the date first stated above.

BELLEROPHON THERAPEUTICS LLC

By: /s/ Jonathan M. Peacock
Name: Jonathan M. Peacock
Title: President and Chief Executive Officer

[Signature Page to Plan of Conversion]

Exhibit 2.2

AGREEMENT AND PLAN OF MERGER

THIS AGREEMENT AND PLAN OF MERGER (this "**Agreement**") is dated as of February 12, 2015, by and among Bellerophon Therapeutics, Inc., a Delaware corporation (the "**Company**"), New Mountain Partners II (AIV-B), L.P., a limited partnership organized under the laws of Delaware ("**New Mountain**"), New Mountain Partners II Special (AIV-A), L.P., a Delaware limited partnership ("**New Mountain Blocker**"), ARCH Venture Fund VI, L.P., a limited partnership organized under the laws of Delaware ("**ARCH Ventures**"), IRDO Holding Corp., a Delaware corporation ("**IRDO**"), Venrock Associates IV, L.P., a limited partnership organized under the laws of Delaware ("**Venrock Associates**"), Venrock Partners, L.P., a limited partnership organized under the laws of Delaware ("**Venrock Partners**"), and Venrock Entrepreneurs Fund IV, L.P., a limited partnership organized under the laws of Delaware ("**Venrock Entrepreneurs**" and, together with Venrock Associates and Venrock Partners, "**Venrock**"), Venrock IK Holdings BT, Inc., a Delaware corporation ("**Venrock Blocker**"), 5AM Ventures LLC, a limited liability company organized under the laws of Delaware ("**5AM Ventures**"), and 5AM Co-Investors LLC, a limited liability company organized under the laws of Delaware ("**5AM Co-Investors**" and, together with 5AM Ventures, "**5AM**"), and 5AM-BT, Inc., a Delaware corporation ("**5AM-BT**"). The Company, New Mountain, New Mountain Blocker, ARCH Ventures, IRDO, Venrock, Venrock Blocker, 5AM and 5AM-BT are collectively referred to herein as the "**Parties**," and each individually is referred to herein as a "**Party**." All references to the Company include its predecessor, Bellerophon Therapeutics LLC, a Delaware limited liability company.

RECITALS

WHEREAS, in anticipation of the initial public offering of the Company, on the date hereof, the Company has previously completed a conversion (the "**Conversion**") from a limited liability company to a corporation,

WHEREAS, (i) the board of directors of the Company and the general partner of New Mountain Blocker deem it advisable that New Mountain Blocker merge with and into the Company (the "**New Mountain Blocker Merger**"), (ii) the board of directors of the Company and the board of directors of IRDO deem it advisable that IRDO merge with and into the Company (the "**IRDO Merger**"), (iii) the board of directors of the Company and the board of directors of Venrock Blocker deem it advisable that Venrock Blocker merge with and into the Company (the "**Venrock Blocker Merger**") and (iv) the board of directors of the Company and the board of directors of 5AM-BT deem it advisable that 5AM-BT merge with and into the Company (the "**5AM-BT Merger**," and collectively with the New Mountain Blocker Merger, IRDO Merger, Venrock Blocker Merger and 5AM-BT Merger, the "**Mergers**"), in each case, upon the terms and subject to the conditions set forth herein and in accordance with Delaware Law;

WHEREAS, the board of managers, board of directors or general partner, as applicable, and, if applicable, the equityholders of each of the Company, New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT have approved the New Mountain Blocker Merger, IRDO Merger, Venrock Blocker Merger and 5AM-BT Merger, as applicable, in accordance with the requirements of Delaware Law and their respective organizational documents; and

WHEREAS, the Parties intend that each of the Mergers qualifies as a "reorganization" within the meaning of Section 368 of the Code and the rules and regulations promulgated thereunder and that this Agreement shall constitute a "plan of reorganization" within the meaning of Treasury Regulation Section 1.368-2(g) with respect to each Merger.

NOW, THEREFORE, in consideration of the premises and of the mutual covenants and agreements contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, hereby agree as follows:

ARTICLE I

Definitions

1.1 Definitions. As used herein, the following terms have the following meanings:

"**Affiliate**" means, with respect to any Person, any Person directly or indirectly controlling, controlled by, or under common control with such other Person. For purposes of this definition, "control" when used with respect to any Person means the power to direct the management and policies of such Person, directly or indirectly, whether through the ownership of voting securities, by contract or otherwise, and the terms "**controlling**" and "**controlled**" have meanings correlative to the foregoing. Notwithstanding the foregoing, for purposes of this Agreement, neither the Company nor any of its Subsidiaries shall be considered an Affiliate of any of the other Parties to this Agreement.

"**Business Day**" means a day, other than Saturday, Sunday or other day on which commercial banks in New York, New York are authorized or required by applicable Law to close.

"**Closing Date**" means the date of the Closing.

"**Code**" means the United States Internal Revenue Code of 1986, as amended.

"**Common Stock**" means the Company's Voting Common Stock, par value $0.01, with the rights, preferences and privileges as described in the Company's certificate of incorporation.

"**Delaware Law**" means, collectively, the DGCL and the DRULPA.

"**DGCL**" means the General Corporation Law of the State of Delaware.

"**DRULPA**" means the Revised Uniform Limited Partnership Act of the State of Delaware.

"**Law**" means any law, statute, regulation, rule, permit, license, certificate, judgment, order, award or other legally binding decision or requirement of any arbitrator, court, government or governmental agency or instrumentality (domestic or foreign).

"**Lien**" means, with respect to any property or asset, any mortgage, lien, pledge, charge or security interest in respect of such property or asset.

"**Material Adverse Effect**" means a material adverse effect on (i) the business, assets or results of operations of the applicable Merged Entity, taken as a whole, or (ii) the ability of the applicable Merged Entity to consummate the transactions contemplated by the Transaction Documents.

"**Merged Entities**" means New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT, and the term "Merged Entity" means any one of them, as the case may be.

"**Permitted Liens and Exceptions**" means Liens for Taxes, assessments and similar charges that are not yet due and payable.

"**Person**" means an individual, corporation, partnership, limited liability company, association, trust or other entity or organization, including a government or political subdivision or an agency or instrumentality thereof.

"**Pre-Closing Tax Period**" means any Tax period ending on or before the Closing Date.

"**Subsidiary**" means any entity of which securities or other ownership interests having ordinary voting power to elect a majority of the board of directors or other persons performing similar functions are at the time directly or indirectly owned by a Person.

"**Tax**" means (1) any tax or other governmental fee or like assessment or charge in the nature of a tax; including, but not limited to, withholding on amounts paid to or by any Person, federal and state income taxes, real property gains taxes, sales and use taxes, escheat taxes, abandoned or unclaimed property taxes, ad valorem taxes, excise taxes, franchise taxes, gross receipts taxes, business license taxes, capital stock taxes, real and personal property taxes, environmental taxes, transfer taxes, severance taxes, alternative or add-on minimum taxes, and custom duties, together with any interest, penalty, addition to tax or additional amount imposed by any governmental authority (whether federal, state, local, municipal, foreign or otherwise) responsible for the imposition of any such tax (a "**Taxing Authority**") and (2) any liability for the payment of any amount of the type described in the immediately preceding clause (1) as a result of a Merged Entity being a member of an affiliated, consolidated or combined group with any other corporation at any time on or prior to the Closing Date.

"**Transaction Documents**" means this Agreement and the Exhibits attached hereto.

"**Voting Agreement**" means that certain Voting Agreement, dated February 12, 2014, by and among the Company, New Mountain Partners II (AIV-A), L.P., New Mountain Affiliated Investors II, L.P., Allegheny New Mountain Partners, L.P., IRDO, Venrock Blocker, Linde North America, Inc., 5AM-BT and Aravis Venture I L.P.

Each of the following terms is defined in the Section set forth opposite such term:

Term	Section
5AM	Preamble
5AM Co-Investors	Preamble
5AM Ventures	Preamble
5AM-BT	Preamble
5AM-BT Merger	Recitals
ARCH Ventures	Preamble
Agreement	Preamble
Certificate of Merger	2.1(b)
Claim	7.3(a)
Closing	2.2
Company	Preamble
Conversion	Recitals
Damages	7.2(a)
Indemnified Party	7.3(a)
Indemnifying Party	7.3(a)
IRDO	Preamble
IRDO Merger	Recitals
Merger Effective Time	2.1(b)
Mergers	Recitals
New Mountain	Preamble
New Mountain Blocker	Preamble
New Mountain Blocker Merger	Recitals
Parties	Preamble
Party	Preamble
Potential Contributor	7.4
Registration Statement	2.1(b)
Returns	3.11
Securities	3.5
Surviving Company	2.1(a)
Third Party Claim	7.3(b)
Transfer Taxes	6.1(b)
Venrock	Preamble
Venrock Blocker	Preamble
Venrock Blocker Merger	Recitals
Venrock Associates	Preamble
Venrock Entrepreneurs	Preamble
Venrock Partners	Preamble
Warranty Breach	7.2(a)

1.2 Other Definitional and Interpretative Provisions. The words "**hereof**," "**herein**," and "**hereunder**" and words of like import used in this Agreement shall refer to this Agreement as a

whole and not to any particular provision of this Agreement. The captions herein are included for convenience of reference only and shall be ignored in the construction or interpretation hereof. References to Articles, Sections, and Exhibits are to Articles, Sections, and Exhibits of this Agreement unless otherwise specified. All Exhibits annexed hereto or referred to herein are hereby incorporated in and made a part of this Agreement as if set forth in full herein. Any capitalized terms used in any Exhibit but not otherwise defined therein, shall have the meaning as defined in this Agreement. Any singular term in this Agreement shall be deemed to include the plural, and any plural term the singular. Whenever the words "**include**," "**includes**," or "**including**" are used in this Agreement, they shall be deemed to be followed by the words "**without limitation**," whether or not they are in fact followed by those words or words of like import. "**Writing**," "**written**," and comparable terms refer to printing, typing and other means of reproducing words (including electronic media) in a visible form. References to any agreement or contract are to that agreement or contract as amended, modified or supplemented from time to time in accordance with the terms hereof and thereof. References to any Person include the successors and permitted assigns of that Person. References from or through any date mean, unless otherwise specified, from and including or through and including, respectively. References to "**law**," "**laws**," or to a particular statute or law shall be deemed also to include any and all Laws.

ARTICLE II

The Mergers And Other Transactions

2.1 The Mergers.

(a) At the Merger Effective Time (as defined below), and in accordance with the applicable provisions of this Agreement and Delaware Law, each of New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT shall be merged with and into the Company. Following the Mergers, the separate corporate or limited partnership existence, as applicable, of each of New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT shall cease and the Company shall continue as the surviving company (the "**Surviving Company**").

(b) At the time determined by the Company, promptly following the Conversion and prior to the effectiveness of the Company's registration statement on Form S-1 (File No. 333-201474) (the "**Registration Statement**") filed with the Securities and Exchange Commission pursuant to the Securities Act of 1933, as amended, the Company shall cause a certificate of merger in form and substance as set forth on Exhibit A attached hereto (the "**Certificate of Merger**") to be executed, acknowledged and filed with the Secretary of State of the State of Delaware, all as provided for and in accordance with Section 251 and Section 264 of the DGCL and Section 17-211 of the DRULPA. The Mergers shall become effective at the time and date as provided under Delaware Law and as specified in the Certificate of Merger (the "**Merger Effective Time**"). References to the Company after the Merger Effective Time shall mean the Surviving Company.

(c) Each Merger shall have the effects set forth under Delaware Law. Without limiting the generality of the foregoing, and subject thereto, at the Merger Effective Time, all the properties, rights, privileges, and powers of each of New Mountain Blocker, IRDO, Venrock

Blocker and 5AM-BT shall vest in the Surviving Company, and all debts, liabilities, and duties of each of New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT shall become the debts, liabilities and duties of the Surviving Company. Notwithstanding the foregoing, it is hereby acknowledged and agreed that, upon consummation of the Mergers, the respective rights and obligations of IRDO, Venrock Blocker and 5AM-BT under the Voting Agreement shall be transferred to ARCH Ventures, Venrock and 5AM, respectively, in accordance with the terms thereof.

(d) The certificate of incorporation and bylaws of the Company, as in effect immediately prior to the Merger Effective Time, shall be the certificate of incorporation and bylaws of the Surviving Company until thereafter amended in accordance with the provisions thereof and applicable Law.

(e) Subject to applicable Law, (i) the directors of the Company immediately prior to the Merger Effective Time shall be the initial directors of the Surviving Company and shall hold office until their respective successors are duly elected and qualified, or their earlier death, resignation, or removal, and (ii) the officers of the Company immediately prior to the Merger Effective Time shall be the initial officers of the Surviving Company and shall hold office until their respective successors are duly elected and qualified, or their earlier death, resignation, or removal.

(f) All of the equity interests of each of New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT outstanding as of immediately prior to the Merger Effective Time shall, as of the Merger Effective Time, by virtue of the Merger and without any action on the part of any Party hereto or the holder thereof or any other Person, be canceled and extinguished and converted into the right to receive the consideration specified in Section 2.1(g). All of such outstanding equity interests of New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT when so converted, shall no longer be outstanding and shall automatically be canceled and the former holders thereof shall cease to have any rights with respect thereto, except the right to receive the consideration specified in Section 2.1(g).

(g) At the Merger Effective Time:

(i) In respect of the outstanding equity interests of New Mountain Blocker held by New Mountain immediately prior to the Merger Effective Time and canceled and extinguished by virtue of the New Mountain Blocker Merger, New Mountain shall receive the number of shares of Common Stock equal to the number of shares of Common Stock held by New Mountain Blocker immediately prior to the New Mountain Blocker Merger, and such shares of Common Stock of the Company received pursuant to the New Mountain Blocker Merger shall be free and clear of all security interests, claims, liens, equities or other encumbrances;

(ii) In respect of the outstanding equity interests of IRDO held by ARCH Ventures immediately prior to the Merger Effective Time and canceled and extinguished by virtue of the IRDO Merger, ARCH Ventures shall receive the number of shares of Common Stock equal to the number of shares of Common Stock held by IRDO immediately prior to the Merger Effective Time, and such shares of Common Stock received pursuant to the IRDO

Merger shall be free and clear of all security interests, claims, liens, equities or other encumbrances;

(iii) In respect of the outstanding equity interests of Venrock Blocker held by Venrock Associates, Venrock Entrepreneurs and Venrock Partners immediately prior to the Merger Effective Time and canceled and extinguished by virtue of the Venrock Blocker Merger, Venrock Associates, Venrock Entrepreneurs and Venrock Partners shall receive the number of shares of Common Stock in the aggregate equal to the number of shares of Common Stock held by Venrock Blocker immediately prior to the Merger Effective Time (with such shares of Common Stock allocated among Venrock Associates, Venrock Entrepreneurs and Venrock Partners in accordance with the allocations set forth on Schedule 2.1(g)(iii) hereto), and such shares of Common Stock received pursuant to the Venrock Blocker Merger shall be free and clear of all security interests, claims, liens, equities or other encumbrances; and

(iv) In respect of the outstanding equity interests of 5AM-BT held by 5AM Ventures and 5AM Co-Investors immediately prior to the Merger Effective Time and canceled and extinguished by virtue of the 5AM-BT Merger, 5AM Ventures and 5AM Co-Investors shall receive the number of shares of Common Stock in the aggregate equal to the number of shares of Common Stock held by 5AM-BT immediately prior to the Merger Effective Time (with such shares of Common Stock allocated between 5AM Ventures and 5AM Co-Investors in accordance with the allocations set forth on Schedule 2.1(g)(iv) hereto), and such shares of Common Stock received pursuant to the 5AM-BT Merger shall be free and clear of all security interests, claims, liens, equities or other encumbrances.

(h) By their execution of this Agreement, New Mountain, as the sole limited partner of New Mountain Blocker, ARCH Ventures, as the sole stockholder of IRDO, Venrock as the sole stockholder of Venrock Blocker and 5AM as the sole stockholder of 5AM-BT, each waives its right to any dissent to the New Mountain Blocker Merger, the IRDO Merger, the Venrock Blocker Merger and the 5AM-BT Merger, respectively, and demand appraisal for its shares of New Mountain Blocker, IRDO, Venrock Blocker and 5AM-BT, respectively, under the DGCL, or otherwise.

2.2 Closing. The closing (the "**Closing**") of the transactions contemplated hereunder shall take place at the offices of Wilmer Cutler Pickering Hale and Dorr LLP, 60 State Street, Boston, Massachusetts 02109. At the Closing:

(i) The Certificate of Merger shall be filed pursuant to the terms of Section 2.1.

(ii) Each of the Parties shall deliver such other documents, instruments and agreements as are required to be delivered by such Party at the Closing pursuant to this Agreement.

2.3 Contribution of Cash. Prior to the Merger Effective Time, if any Merged Entity does not have an amount of cash sufficient to pay all liabilities of such Merged Entity (as estimated in good faith by each Merged Entity), including Taxes for any Pre-Closing Tax Period, the equity holders of such Merged Entity shall contribute an amount of cash to such Merged Entity such

that following such contribution, the Merged Entity will have an amount of cash sufficient to pay all such liabilities.

2.4 Payment of Indebtedness. No later than immediately prior to the Closing, each Merged Entity shall repay all indebtedness for borrowed money (including any capital leases) of such Merged Entity outstanding immediately prior to the Closing, of any kind or nature whatsoever, including any obligations related thereto (including any accrued interest or prepayment penalties). At Closing, each Merged Entity shall deliver the Company customary payoff letters from each holder of any indebtedness of such Merged Entity to be repaid at the Closing.

ARTICLE III

Representations And Warranties Of The Merged Entities

Each of the Merged Entities, severally and not jointly, represents and warrants to the Company as of the date hereof that:

3.1 Corporate Existence and Power. Such Merged Entity is a corporation or limited partnership duly incorporated or organized, as applicable, validly existing and in good standing under the laws of its jurisdiction of incorporation or organization, as applicable, with full power and authority to conduct its business as it is now being conducted and to own or use the properties and assets that it purports to own or use.

3.2 Authorization. The execution, delivery and performance by such Merged Entity of the Transaction Documents to which it is or will be a party and the consummation of the transactions contemplated thereby are within the corporate or limited partnership powers and authority, as applicable, of such Merged Entity and have been duly authorized by all necessary corporate or limited partnership action, as applicable, on the part of such Merged Entity. Each of the Transaction Documents to which it is or will be a party constitutes, or will when executed constitute, the legal, valid and binding obligation of such Merged Entity enforceable against such Merged Entity in accordance with its respective terms, (a) except as enforcement may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws now or hereafter in effect relating to or affecting creditors' rights generally, including the effect of statutory and other laws concerning fraudulent conveyances and preferential transfers and (b) subject to the limitations imposed by general equitable principles (regardless of whether such enforceability is considered in proceeding at law or in equity).

3.3 Governmental Authorization. The execution, delivery and performance by such Merged Entity of each of the Transaction Documents to which it is or will be a party and the consummation of the transactions contemplated thereby require no action, consent or approval by or in respect of, filing with or notice to, any governmental body, agency or official other than the Certificate of Merger and any other such action or filing as to which the failure to make or obtain would not have, individually or in the aggregate, a Material Adverse Effect.

3.4 Noncontravention. The execution, delivery and performance by such Merged Entity of any of the Transaction Documents to which it is or will be a party, and the consummation of the transactions contemplated thereby do not and will not (a) violate or conflict with the

organizational documents of such Merged Entity or any resolution adopted by or any action taken by the board of directors, board of managers, general partner or equityholders of such Merged Entity, (b) assuming compliance with the matters referred to in Section 3.3, contravene or conflict with or constitute a violation of any provision of any Law binding upon or applicable to such Merged Entity, (c) with or without the giving of notice or the lapse of time, or both, constitute a default under or give rise to any right of termination, cancellation or acceleration of any right or obligation of such Merged Entity, or to a loss of any benefit to which such Merged Entity is entitled, under any provision of any agreement, contract or other instrument to which such Party is a party or by which it or its properties or assets is bound or (d) result in the creation or imposition of any Lien (other than Permitted Liens and Exceptions) upon or with respect to such Merged Entity or its assets.

3.5 Capitalization. New Mountain Blocker represents and warrants that New Mountain owns 100% of the limited partnership interests of New Mountain Blocker. IRDO represents and warrants that ARCH Ventures owns 100% of the issued and outstanding capital stock of IRDO. Venrock Blocker represents and warrants that Venrock owns 100% of the issued and outstanding capital stock of Venrock Blocker. 5AM-BT represents and warrants that 5AM owns 100% of the issued and outstanding capital stock of 5AM-BT. All of the capital stock or equity interests, as applicable, of such Merged Entity have been duly authorized and validly issued and are fully paid and non-assessable. Other than the capital stock or equity interests issued to New Mountain (and the general partnership interest in New Mountain Blocker held by the general partner of New Mountain Blocker), ARCH Ventures, Venrock or 5AM described in this Section 3.5, there are no outstanding (a) capital stock or equity interests or other voting securities of such Merged Entity, (b) securities of such Merged Entity convertible into or exchangeable for capital stock or equity interests or other voting securities of such Merged Entity or (c) options or other rights to acquire from such Merged Entity, or other obligation of such Merged Entity to issue, any capital stock or equity interests or other voting securities of such Merged Entity or securities convertible into or exchangeable for capital stock or equity interests or other voting securities of such Merged Entity (the items in clauses (a) through (c) being referred to collectively as the "Securities"). There are no outstanding obligations of such Merged Entity to repurchase, redeem or otherwise acquire any Securities and there are no agreements or other instruments relating to the issuance, sale or transfer by such Merged Entity of any Securities.

3.6 Subsidiaries. Such Merged Entity has no Subsidiaries. Such Merged Entity does not control directly or indirectly or have any direct or indirect equity participation in any corporation, partnership, trust, or other business association (other than the Company).

3.7 No Undisclosed Material Liabilities. Such Merged Entity does not conduct any operating or other business or related general business operations, other than its activities as a holding company incident to its direct or indirect ownership of equity interests of the Company. Such Merged Entity does not have any liabilities of any kind, character or description (whether known or unknown, accrued, absolute, contingent or otherwise), other than (a) deferred income Taxes that reflect only timing differences between the treatment of items for accounting and income tax purposes, and (b) income Taxes with respect to Pre-Closing Tax Periods that are not yet due and payable.

3.8 Related Party Agreements. Except as otherwise provided in the Transaction Documents, there are no agreements, contracts, commitments or understandings, other than any such agreements, contracts, commitments or understandings that will be terminated as of Closing without any further liability or obligation on the part of such Merged Entity, by and between such Merged Entity, on the one hand, and such Merged Entity's Affiliates, on the other hand, including, without limitation, any such agreements, contracts, commitments or understandings pursuant to which such Affiliate provides or receives any information, assets, properties, support or other services to or from such entity.

3.9 Litigation. There is no claim, action, suit, investigation or proceeding pending against or, to the knowledge of such Merged Entity, threatened against, such Merged Entity or any of its assets before any court or arbitrator or any governmental body, agency or official. As of the date hereof, such Merged Entity is not aware of any claim, action, suit investigation or proceeding pending or threatened against such Merged Entity or any of its assets, or any orders or decrees binding on such Merged Entity or any of its assets.

3.10 Compliance with Laws. Such Merged Entity is, and at all times since the date of its incorporation or formation, as applicable, has been, in compliance with all applicable Laws.

3.11 Taxes. Each Merged Entity, severally and not jointly, represents and warrants to the Company as of the date hereof that (a) all Tax returns, statements, reports and forms (collectively, "**Returns**") that are material and are required to be filed with any Taxing Authority by, or with respect to, such Merged Entity on or before the Closing Date (taking into account any duly obtained extensions) have been, or will be, timely filed, (b) such Merged Entity has timely paid all Taxes due and payable by such Merged Entity shown as due and payable on the Returns that have been filed, (c) the Returns that have been filed are true, correct and complete in all material respects, (d) there is no action, suit, proceeding, investigation, audit or claim now proposed (to such Merged Entity's knowledge) or pending against or with respect to such Merged Entity in respect of any material Tax, (e) such Merged Entity has properly withheld and paid all Taxes required to have been withheld and paid in connection with amounts paid or owing to any equityholder, employee, creditor, independent contractor, or other third party, (f) there is no claim pending or to such Merged Entity's knowledge, proposed or threatened by a Taxing Authority, in a jurisdiction where such Merged Entity does not file Returns that such Merged Entity is or may be subject to taxation in such jurisdiction, (g) assuming the applicable Merger qualifies as Tax-free, such Merged Entity has no liability for Taxes for any Pre-Closing Tax Period in excess of the amount of cash retained by the respective Merged Entity pursuant to Section 2.3 to pay such Taxes, (h) such Merged Entity has not received any notice in writing from a Taxing Authority of any proposed or pending action, suit, proceeding, investigation, audit or claim with respect to such Merged Entity in respect of any Tax, and (i) such Merged Entity has not consented to extend the time, nor is the beneficiary of any extension of time, in which any Tax may be assessed or collected by any Taxing Authority.

3.12 Inspections; No Other Representations. No Merged Entity makes any express or implied representations or warranties of any nature, whether in writing, oral or otherwise, made by or on behalf of or imputed to any Merged Entity or any of its Affiliates, except as expressly set forth in this Agreement. Without limiting the generality of the foregoing, no Merged Entity nor any of its Affiliates makes any representation or warranty with respect to any projections,

estimates or budgets delivered to or made available to the Company of future revenues, future results of operations (or any component thereof), future cash flows or future financial condition (or any component thereof) or any other information or documents made available to the Company or its counsel, accountants or advisors with respect to any Merged Entity or any of the foregoing business, assets, liabilities or operations.

ARTICLE IV

Representations And Warranties Of The Company

The Company represents and warrants to each of the other Parties, as of the date hereof, that:

4.1 Corporate Existence and Power. The Company is a corporation duly incorporated, validly existing and in good standing under the laws of its jurisdiction of incorporation, with full power and authority to conduct its business as it is now being conducted and to own or use the properties and assets that it purports to own or use. The shares of Common Stock to be issued by the Company in the Mergers will be duly authorized, validly issued, fully paid and non-assessable.

4.2 Corporate Authorization. The execution, delivery and performance by the Company of the Transaction Documents to which it is or will be a party and the consummation of the transactions contemplated thereby are within the corporate powers and authority of the Company and have been duly authorized by all necessary corporate action on the part of the Company. Each of the Transaction Documents to which the Company is or will be a party constitutes, or will when executed constitute, the legal, valid and binding obligation of the Company, enforceable against the Company in accordance with its respective terms, (a) except as enforcement may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws now or hereafter in effect relating to or affecting creditors' rights generally, including the effect of statutory and other laws concerning fraudulent conveyances and preferential transfers, and (b) subject to the limitations imposed by general equitable principles (regardless of whether such enforceability is considered in a proceeding at law or in equity).

4.3 Governmental Authorization. The execution, delivery and performance by the Company of each of the Transaction Documents to which it is or will be a party and the consummation of the transactions contemplated thereby require no action, consent or approval by or in respect of, filing with or material notice to, any governmental body, agency or official other than: (a) the filing of the Certificate of Merger; and (b) any other such action or filing as to which the failure to make or obtain would not have, individually or in the aggregate, a material adverse effect on the ability of the Company to consummate the transactions contemplated by the Transaction Documents.

4.4 Noncontravention. The execution, delivery and performance by the Company of any of the Transaction Documents to which it is or will be a party and the consummation of the transactions contemplated thereby do not and will not (a) violate or conflict with the certificate of incorporation of the Company or any resolution adopted by or any action taken by the board of directors or stockholders of the Company, (b) assuming compliance with the matters referred

to in Section 4.3, contravene or conflict with or constitute a violation of any provision of any Law binding upon or applicable to the Company, (c) with or without the giving of notice or the lapse of time, or both, constitute a default under or give rise to any right of termination, cancellation or acceleration of any right or obligation of the Company, or to a loss of any benefit to which the Company is entitled under any provision of any agreement, contract or other instrument to which the Company is a party or by which the Company or its properties or assets are bound or (d) result in the creation or imposition of any Lien (other than Permitted Liens and Exceptions) upon or with respect to the Company or its properties or assets, except, in the case of clauses (b), (c) or (d), for any such contravention, conflict, violation, default, termination, cancellation, acceleration or loss that would not have, individually or in the aggregate, a material adverse effect on the Company and its Subsidiaries, taken as a whole.

ARTICLE V

Covenants Of The Parties

Each of the Parties hereto agrees that:

5.1 Reasonable Best Efforts; Further Assurances. Subject to the terms and conditions of this Agreement, each Party will use its reasonable best efforts to take, or cause to be taken, all actions and to do, or cause to be done, all things necessary or desirable to consummate the transactions contemplated by any of the Transaction Documents. Each Party shall execute and deliver such other documents, certificates, agreements and other writings and to take such other actions as may be necessary or appropriate in order to consummate or implement expeditiously the transactions contemplated by any of the Transaction Documents.

5.2 Public Announcements. Other than the Company, none of the other Parties hereto may issue any press release or make any public statement with respect to any Transaction Document or the transactions contemplated thereby.

ARTICLE VI

Tax Matters

6.1 Tax Covenants

(a) The Company shall prepare and timely file all Returns that are required to be filed after the Closing reflecting the income of each Merged Entity for all Pre-Closing Tax Periods. No later than thirty (30) days prior to filing any such Return, the Company shall submit such Return to New Mountain (in the case of New Mountain Blocker), ARCH Ventures (in the case of IRDO), Venrock (in the case of Venrock Blocker) and 5AM (in the case of 5AM-BT) for review and consent. If an amount of Taxes due with such Return that is less than the amount of cash that was held by the respective Merged Entity immediately prior to the Closing (after giving effect to the other liabilities, if any, of such Merged Entity immediately prior to the Closing), then within ten (10) Business Days after filing the applicable Return, the Company shall pay the amount of such excess cash to New Mountain (in the case of New Mountain Blocker), ARCH Ventures (in

the case of IRDO), Venrock (in the case of Venrock Blocker) and 5AM (in the case of 5AM-BT).

(b) Returns related to any transfer, documentary, sales, use, stamp, registration and other such Taxes and fees (including any penalties and interest) incurred in connection with the Mergers (all such Taxes, "**Transfer Taxes**") shall be filed by the Party required to file such Returns under applicable Law and such Party shall pay the Transfer Taxes shown thereon. The provisions of this Section 6.1(b), and no other provision, will govern the allocation between the parties of the economic burden of Transfer Taxes.

6.2 Pre-Closing Tax Refunds. New Mountain, ARCH Ventures, Venrock or 5AM shall be entitled to any Tax refunds attributable to any Pre-Closing Tax Period of New Mountain Blocker, IRDO, Venrock Blocker, or 5AM-BT, respectively, and the Company shall promptly pay by wire transfer of immediately available funds any such refunds to New Mountain, ARCH Ventures, Venrock or 5AM, as the case may be, less any applicable Taxes, withholdings or reasonable expenses, after receipt thereof. If New Mountain Blocker, IRDO, Venrock Blocker or 5AM-BT has a net operating loss for a Pre-Closing Tax Period, the Company shall carryback such loss pursuant to Section 172 of the Code and file a claim for refund on IRS Form 1139 with respect to such carryback and promptly pay by wire transfer of immediately available funds such refund to New Mountain, ARCH Ventures, Venrock or 5AM, as the case may be, after receipt thereof. The Company shall file for, at the request of New Mountain, ARCH Ventures, Venrock or 5AM, and use reasonable commercial efforts to obtain any refund to which New Mountain, ARCH Ventures, Venrock or 5AM, as the case may be, is entitled under this section.

6.3 Tax Reporting. The Parties agree to treat, for U.S. federal, state and local Tax purposes, the transactions contemplated by this Agreement and the Plan of Conversion entered into by the Company in connection with the Conversion as governed by Sections 351 and 368 of the Code and report consistently with such treatment for all U.S. federal, state and local Tax purposes.

ARTICLE VII

Survival; Indemnification

7.1 Survival. The representations and warranties of any of the Parties hereto contained in this Agreement shall survive the Closing Date and shall expire on the date that is one year following the Closing Date. Except as otherwise provided in this Agreement, the covenants and agreements of the Parties contained in this Agreement shall survive Closing and shall continue in full force and effect indefinitely or for the shorter period specified in this Agreement. Any breach of representation, warranty, covenant or agreement in respect of which indemnity may be sought under this Agreement shall survive the time at which it would otherwise terminate pursuant to this Section 7.1 if notice of the inaccuracy or breach thereof giving rise to such right of indemnity shall have been given to the Party against whom such indemnity may be sought prior to such time.

7.2 Indemnification.

(a) From and after Closing, the Company hereby indemnifies New Mountain, ARCH Ventures, Venrock and 5AM against and agrees to hold each of them harmless from (i) any and all damage, loss, liability and expense (including, without limitation, reasonable expenses of investigation and reasonable attorneys' fees and expenses in connection with any action, suit or proceeding) ("**Damages**") actually incurred or suffered by New Mountain, ARCH Ventures, Venrock or 5AM, as applicable, arising out of or resulting from any inaccuracy or breach of any representation and warranty (each such inaccuracy and breach, a "**Warranty Breach**") or breach of a covenant, in each case of the Company contained in the Transaction Documents or in the exhibits, schedules or certificates to, or delivered in connection with, the Transaction Documents or (ii) any and all Damages incurred or suffered by New Mountain, ARCH Ventures, Venrock or 5AM, as applicable, on account of the gross negligence, intentional misrepresentation, willful misconduct or fraud of the Company.

(b) From and after Closing, New Mountain hereby indemnifies the Company against and agrees to hold it harmless from (i) any and all Damages actually incurred or suffered by the Company arising out of or related in any way to any Warranty Breach or breach of a covenant, in each case of New Mountain or New Mountain Blocker contained in the Transaction Documents or in the exhibits, schedules or certificates to, or delivered in connection with, the Transaction Documents or (ii) any and all Damages incurred or suffered by the Company on account of the gross negligence, intentional misrepresentation, willful misconduct or fraud of New Mountain or New Mountain Blocker.

(c) From and after Closing, ARCH Ventures hereby indemnifies the Company against and agrees to hold it harmless from (i) any and all Damages actually incurred or suffered by the Company arising out of or related in any way to any Warranty Breach or breach of a covenant, in each case of ARCH Ventures or IRDO contained in the Transaction Documents or in the exhibits, schedules or certificates to, or delivered in connection with, the Transaction Documents or (ii) any and all Damages incurred or suffered by the Company on account of the gross negligence, intentional misrepresentation, willful misconduct or fraud of ARCH Ventures or IRDO.

(d) From and after Closing, Venrock hereby indemnifies the Company against and agrees to hold it harmless from (i) any and all Damages actually incurred or suffered by the Company arising out of or related in any way to any Warranty Breach or breach of a covenant, in each case of Venrock or Venrock Blocker contained in the Transaction Documents or in the exhibits, schedules or certificates to, or delivered in connection with, the Transaction Documents or (ii) any and all Damages incurred or suffered by the Company on account of the gross negligence, intentional misrepresentation, willful misconduct or fraud of Venrock or Venrock Blocker.

(e) From and after Closing, 5AM hereby indemnifies the Company against and agrees to hold it harmless from (i) any and all Damages actually incurred or suffered by the Company arising out of or related in any way to any Warranty Breach or breach of a covenant, in each case of 5AM or 5AM-BT contained in the Transaction Documents or in the exhibits, schedules or certificates to, or delivered in connection with, the Transaction Documents or (ii) any and all Damages incurred or suffered by the Company on account of the gross negligence, intentional misrepresentation, willful misconduct or fraud of 5AM or 5AM-BT.

(f) Notwithstanding anything contained in this Agreement to the contrary, other than in the case of a claim based on gross negligence, intentional misrepresentation, willful misconduct or fraud, no Party shall be entitled to seek, nor be entitled to, incidental, indirect punitive, special or consequential damages (including damages for any lost profits) in any Claim for indemnification or recovery of Damages pursuant to this Agreement unless such type of damages are sought against such Party by an unaffiliated or unrelated third party.

7.3 Procedures.

(a) The Party seeking indemnification under Section 7.2 (the "**Indemnified Party**") agrees to give prompt notice to the Party against whom indemnity is sought (the "**Indemnifying Party**") of the assertion of any claim, or the commencement of any suit, action or proceeding ("**Claim**") in respect of which indemnity may be sought under such Section and will promptly provide the Indemnifying Party such information and access to personnel with respect thereto that the Indemnifying Party may reasonably request. The failure to so notify the Indemnifying Party shall not relieve the Indemnifying Party of its obligations hereunder, except to the extent such failure shall have adversely prejudiced the Indemnifying Party.

(b) The Indemnified Party shall obtain the prior written consent of the Indemnifying Party (which shall not be unreasonably withheld, conditioned or delayed) before entering into any settlement of any Claim asserted by any third party ("**Third Party Claim**").

(c) Each Party shall cooperate, and cause their respective Affiliates to cooperate, in the defense or prosecution of any Third Party Claim and shall furnish or cause to be furnished such records, information and testimony, and attend such conferences, discovery proceedings, hearings, trials or appeals, as may be reasonably requested in connection therewith.

(d) Each Indemnified Party must mitigate in accordance with applicable Law any loss for which such Indemnified Party seeks indemnification under this Agreement. If such Indemnified Party mitigates its loss after the Indemnifying Party has paid the Indemnified Party under any indemnification provision of this Agreement in respect of that loss, the Indemnified Party must promptly notify the Indemnifying Party and promptly pay to the Indemnifying Party the extent of the value of the benefit (or, if less, the amount of any such loss previously paid by the Indemnifying Party) to the Indemnified Party of that mitigation (less the Indemnified Party's reasonable costs of mitigation).

(e) Each Indemnified Party shall use reasonable efforts to collect any amounts available under insurance coverage or through indemnification, contribution or other reimbursement arrangements from any other Person alleged to be responsible, for any Damages payable under Section 7.2, and the amounts received from such sources shall offset any Damages otherwise payable under Section 7.2

(f) Assignment of Claims. If the Indemnified Party receives any payment from an Indemnifying Party in respect of any Damages pursuant to Section 7.2 and the Indemnified Party could have recovered all or a part of such Damages from a third party (other than any Subsidiary of the Company or any current or former employee or agent of such Persons) (a "**Potential Contributor**") based on the underlying Claim asserted against the Indemnifying Party, the

Indemnified Party shall assign such of its rights to proceed against the Potential Contributor as are necessary to permit the Indemnifying Party to recover from the Potential Contributor the amount of such payment.

7.4 Exclusivity. After the Closing, Article VII will provide the sole and exclusive remedy for any misrepresentation, breach of warranty, covenant or other agreement or other claim arising out of the Transaction Documents or the transactions contemplated thereby, including any claim for gross negligence, intentional misrepresentation, willful misconduct or fraud. Notwithstanding the foregoing, it is understood that nothing herein shall prohibit any Party hereto from exercising its rights to seek equitable relief with respect to a breach of covenant or agreement under any Transaction Document.

ARTICLE VIII

Miscellaneous

8.1 Notices. All notices, requests, or consents required or permitted to be given under this Agreement must be in writing and shall be deemed to have been given (a) three (3) days after the date mailed by registered or certified mail, addressed to the recipient, with return receipt requested, (b) upon delivery to the recipient in person or by courier, or (c) upon receipt of a facsimile or e-mail transmission by the recipient. Such notices, requests and consents shall be given,

if to New Mountain or New Mountain Blocker, to:

c/o New Mountain Capital, L.L.C.
787 Seventh Avenue, 49th Floor
New York, NY 10019
Attn: Adam Weinstein

if to ARCH Ventures or IRDO, to:

c/o ARCH Venture Partners
8725 West Higgins Road
Suite 290
Chicago, IL 60631
Attn: Mark McDonnell

if to Venrock or Venrock Blocker, to:

c/o Venrock Associates
3340 Hillview Avenue
Palo Alto, CA 94304

Attn: Bryan E. Roberts

if to 5AM or 5AM-BT, to:

c/o 5AM Ventures LLC
2200 Sand Hill Road, Suite 1100
Menlo Park, CA 94025
Attn: Andrew Schwab

If to the Company, to:

c/o Bellerophon Therapeutics, Inc.
53 Frontage Road, Suite 301
Hampton, NJ 08827
Attention: Chief Executive Officer

with copies (which shall not constitute notice) to:

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attention: Lia Der Marderosian, Esq.

or to such other address or facsimile number and with such other copies, as such Party may hereafter specify for the purpose by notice to the other Parties.

Whenever any notice is required to be given by Law or this Agreement, a written waiver thereof, signed by the person entitled to notice, whether before or after the time stated therein, shall be deemed equivalent to the giving of such notice. Without limiting the manner by which notice otherwise may be given effectively to the Parties pursuant to this Agreement, any notice to the Parties given by the Company under any provision of this Agreement shall be effective if given by a form of electronic transmission consented to by the Party to whom the notice is given. Any such consent shall be revocable by such Party by written notice to the Company.

8.2 Amendments and Waivers.

(a) Any provision of this Agreement may be amended or waived if, but only if, such amendment or waiver is in writing and is signed, in the case of an amendment, by each Party to this Agreement, or in the case of a waiver, by the Party against whom the waiver is to be effective.

(b) No failure or delay by any Party in exercising any right, power or privilege hereunder shall operate as a waiver thereof nor shall any single or partial exercise thereof preclude any other or further exercise thereof or the exercise of any other right, power or privilege. The rights and remedies herein provided shall be cumulative and not exclusive of any rights or remedies provided by law.

8.3 Expenses. Except to the extent otherwise expressly provided for in any of the Transaction Documents, all costs and expenses incurred by any Party in connection with the negotiation, preparation, execution and delivery of this Agreement and the Transaction Documents and the consummation of the Closing shall be paid by the Party incurring such costs or expenses.

8.4 Successors and Assigns. The provisions of this Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective successors and assigns; provided that no Party may assign, delegate or otherwise transfer any of its rights or obligations under this Agreement without the consent of each other Party hereto.

8.5 Governing Law. This Agreement is governed by and shall be construed in accordance with the law of the State of Delaware, without regard to the conflicts of law rules of such state.

8.6 Consent to Jurisdiction. Except as otherwise expressly provided in this Agreement, the Parties agree that any suit, action or proceeding seeking to enforce any provision of, or based on any matter arising out of or in connection with, any of the Transaction Documents or the transactions contemplated thereby shall be brought in the United States District Court or any Delaware state court sitting in Wilmington, Delaware, so long as one of such courts shall have subject matter jurisdiction over such suit, action or proceeding, and that any cause of action arising out of any of the Transaction Documents shall be deemed to have arisen from a transaction of business in the State of Delaware, and each of the Parties hereby irrevocably consents to the jurisdiction of such courts (and of the appropriate appellate courts therefrom) in any such suit, action or proceeding and irrevocably waives, to the fullest extent permitted by law, any objection that it may now or hereafter have to the laying of the venue of any such suit, action or proceeding in any such court or that any such suit, action or proceeding which is brought in any such court has been brought in an inconvenient forum. Process in any such suit, action or proceeding may be served on any Party anywhere in the world, whether within or without the jurisdiction of any such court. Without limiting the foregoing, each Party agrees that service of process on such Party as provided in Section 8.1 shall be deemed effective service of process on such Party.

8.7 WAIVER OF JURY TRIAL. EACH OF THE PARTIES HERETO HEREBY IRREVOCABLY WAIVES ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF OR RELATED TO THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREBY.

8.8 Counterparts; Third Party Beneficiaries. This Agreement may be signed in any number of counterparts, each of which shall be an original, with the same effect as if the signatures thereto and hereto were upon the same instrument. Each Transaction Document shall become effective when each Party thereto shall have received a counterpart thereof signed by the other Party thereto. No Transaction Document is intended to confer upon any Person other than the Parties thereto any rights or remedies hereunder.

8.9 Entire Agreement. The Transaction Documents constitute the entire agreement between the parties with respect to the subject matter of this Agreement and supersede all prior agreements and understandings, both oral and written, between the parties with respect to the

subject matter of this Agreement. No representation, inducement, promise, understanding, condition or warranty not set forth herein has been made or relied upon by any Party hereto.

8.10 Severability. If any term, provision, covenant or restriction of this Agreement is held by a court of competent jurisdiction or other governmental authority to be invalid, void or unenforceable, the remainder of the terms, provisions, covenants and restrictions of this Agreement shall remain in full force and effect and shall in no way be affected, impaired or invalidated so long as the economic or legal substance of the transactions contemplated hereby is not affected in any manner materially adverse to any Party. Upon such a determination, the Parties shall negotiate in good faith to modify this Agreement so as to effect the original intent of the Parties as closely as possible in an acceptable manner in order that the transactions contemplated hereby be consummated as originally contemplated to the fullest extent possible.

[*Remainder of page intentionally left blank*.]

IN WITNESS WHEREOF, the parties hereto have caused this Agreement and Plan of Merger to be duly executed as of the day and year first above-written.

COMPANY

BELLEROPHON THERAPEUTICS, INC.

By: /s/ Jonathan M. Peacock
Name: Jonathan M. Peacock
Title: President and Chief Executive Officer

[*Signature Page to Agreement and Plan of Merger*]

NEW MOUNTAIN

NEW MOUNTAIN PARTNERS II (AIV-B), L.P.

By: New Mountain Investments II, L.L.C.
Its: General Partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

NEW MOUNTAIN BLOCKER

NEW MOUNTAIN PARTNERS II SPECIAL (AIV-A), L.P.

By: New Mountain Investments II, L.L.C.
Its: General Partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

VENROCK

VENROCK ASSOCIATES IV, L.P.
By: Venrock Management IV, LLC
Its: General Partner

VENROCK PARTNERS, L.P.
By: Venrock Partners Management, LLC
Its: General Partner

VENROCK ENTREPRENEURS FUND IV, L.P.
By: VEF Management IV, LLC
Its: General Partner

By: /s/ Bryan Roberts
Authorized Signatory

VENROCK BLOCKER
Venrock IK Holdings BT, Inc.

By: /s/ David Stepp
Authorized Signatory

[*Signature Page to Agreement and Plan of Merger*]

ARCH

ARCH VENTURE FUND VI, L.P.

By: ARCH Venture Partners VI, L.P.,
Its general partner

By: ARCH Venture Partners VI, LLC,
Its general partner

By: /s/ Robert T. Nelsen
Name: Robert T. Nelsen
Title: Managing Director

IRDO

IRDO Holding Corp.

By: /s/ Mark McDonnell
Name: Mark McDonnell
Title: Secretary

5AM

5AM VENTURES LLC

By: 5AM Partners LLC,
Its manager

By: /s/ Andrew J. Schwab
Name: Andrew J. Schwab
Title: Managing Director

5AM CO-INVESTORS LLC

By: 5AM Partners LLC,
Its manager

By: /s/ Andrew J. Schwab
Name: Andrew J. Schwab
Title: Managing Director

5AM-BT

5AM-BT, INC.

By: /s/ Andrew J. Schwab
Name:
Title:

Exhibit 4.2

STOCKHOLDERS AGREEMENT

This STOCKHOLDERS AGREEMENT, dated as of February 12, 2015, is made and entered into by and among Bellerophon Therapeutics, Inc., a Delaware corporation (formerly Bellerophon Therapeutics LLC, a Delaware limited liability company), and Linde North America, Inc. ("**Linde**"), a Delaware corporation. Capitalized terms shall have the meanings assigned to them in Section 1.

WHEREAS, in anticipation of its public offering, Bellerophon Therapeutics LLC has been converted on the date hereof from a limited liability company into a corporation known as Bellerophon Therapeutics, Inc. (the "**Conversion**"); and

WHEREAS, in connection with the Conversion, the parties have agreed to enter into this Agreement to provide the parties with the rights and obligations set forth in this Agreement.

NOW, THEREFORE, in consideration of the premises and the mutual agreements contained herein, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto hereby agree as follows:

1. Defined Terms.

1.1 Definitions. For purposes of this Agreement, the following terms have the following meanings:

"**Affiliate**" means, (a) with respect to any Person, any other Person which, directly or indirectly, controls, is controlled by or is under common control with such Person, where "**control**" means the possession, directly or indirectly, of the power to direct the management and policies of such Person, whether through the ownership of voting securities, by contract or otherwise, and (b) with respect to any individual, also means the spouse or child of such individual.

"**Agreement**" means this Stockholders Agreement, as the same may be amended, restated, modified or supplemented from time to time.

"**Beneficially Own**" means beneficially own as determined under Rule 13d-3 promulgated under the Securities Exchange Act of 1934, as amended from time to time.

"**Board**" means the board of directors of the Company as it may be composed from time to time in accordance with the Certificate of Incorporation, the Company's bylaws (as in effect from time to time), this Agreement and the General Corporation Law of the State of Delaware (as in effect from time to time).

"**Certificate of Incorporation**" means the Certificate of Incorporation of the Company, as in effect from time to time.

"**Common Stock**" means any shares of common stock, par value $0.01 per share, of the Company, now or hereafter authorized to be issued, and any and all equity interests of any kind whatsoever of the Company which may be issued on or after the date hereof in respect of, in

exchange for, or upon conversion of the Common Stock pursuant to a merger, consolidation, stock split, reverse split, stock dividend, recapitalization of the Company or otherwise.

"**Company**" means Bellerophon Therapeutics, Inc., a Delaware corporation, and shall, to the extent this Agreement survives, include any successor thereto by merger, consolidation, acquisition of substantially all the assets thereof, or otherwise, including any parent or subsidiary thereof that undertakes a Public Offering in lieu of the Company.

"**Convertible Securities**" means (a) any options or warrants to purchase or other rights to acquire Common Stock, (b) any securities by their terms convertible into, or exercisable or exchangeable for, Common Stock (directly or indirectly) and (c) any options or warrants to purchase or other rights to acquire any such convertible, exercisable or exchangeable securities.

"**Initial Public Offering**" means the first Public Offering.

"**Linde Entities**" means Linde, Linde Parent and any Affiliate of any of the foregoing.

"**Linde Holder**" means any of the Linde Entities and any Person that acquires shares of Common Stock from any of the Linde Entities or other Linde Holders in a transaction other than a Public Offering or a sale pursuant to Rule 144.

"**Linde Parent**" means Linde AG, a company incorporated under the laws of Germany.

"**Person**" means any individual, corporation, association, partnership (general or limited), joint venture, trust, estate, limited liability company, organization or other legal entity, or any nation, government, governmental agency or political subdivision thereof, or any person or body exercising executive, legislative, judicial, regulatory, administrative or taxing functions of or pertaining to government, including any court.

"**Public Offering**" means a public offering of equity interests in the Company through a registration statement (other than a Form S-8 or successor forms) filed with, and declared effective by, the United States Securities and Exchange Commission and pursuant to which such equity interests are authorized and approved for listing on a national securities exchange.

"**Rule 144**" means Rule 144 promulgated under the Securities Act of 1933, as amended from time to time.

"**Subsidiary**" means any direct or indirect subsidiary of the Company.

"**Termination Date**" means the first date after the consummation of an Initial Public Offering on which no Linde Holder, together with its Affiliates, Beneficially Owns (a) at least fifty percent (50%) of the sum of (i) the aggregate number of shares of Common Stock Beneficially Owned by the Linde Entities as of immediately prior to the consummation of the Initial Public Offering plus (ii) the aggregate number of shares of Common Stock, if any, acquired by any of the Linde Entities from the Company in connection with or subsequent to the

consummation of the Initial Public Offering and (b) at least ten percent (10%) of the number of shares of Common Stock that were set forth as outstanding on the cover of the Company's then most recently filed Annual Report on Form 10-K or Quarterly Report on Form 10-Q, as the case may be; provided that the Termination Date shall be deemed to have occurred in the event that: (A) a Linde Holder other than any Linde Entity, or any of their respective Affiliates, Beneficially Owns the percentage of shares described in clause (a) of this definition; (B) the rights described in Section 2.2 hereof have not been assigned to such Linde Holder pursuant to Section 3.10 hereof; and (C) the aggregate number of shares of Common Stock then Beneficially Owned by the Linde Entities constitutes less than fifteen percent (15%) of the sum of (x) the aggregate number of shares of Common Stock Beneficially Owned by the Linde Entities as of immediately prior to the consummation of the Initial Public Offering plus (y) the aggregate number of shares of Common Stock, if any, acquired by any of the Linde Entities from the Company in connection with or subsequent to the consummation of the Initial Public Offering.

"**Voting Agreement**" means the Voting Agreement, dated as of February 12, 2014, by and among the Company and the stockholders party thereto from time to time, as the same may be amended, restated, modified or supplemented from time to time.

1.2 Other Defined Terms. The following is a list of the remaining defined terms used in this Agreement:

Term	Section
Assignee	3.10
Conversion	Recitals
Linde	Preamble
Linde Director	2.2(a)
Linde Nominee	2.2(a)

2. Board of Directors.

2.1 Effectiveness and Termination. This Section 2 shall, without further action of any of the parties, (a) become effective concurrently with the termination of the Voting Agreement and (b) terminate automatically and be of no further force and effect at the close of business on the Termination Date.

2.2 Director Nomination Rights.

(a) Linde shall have the right, at any time and from time to time, exercisable by written notice delivered to the Company referencing this Section 2.2, to designate one (1) individual to be appointed to the Board or nominated for election to the Board in each case pursuant to the procedures set forth in this Section 2.2 (each such individual designated by Linde pursuant to this Section 2.2, a "**Linde Nominee**", and any Linde Nominee who is appointed or elected to the Board pursuant to this Section 2.2, a "**Linde Director**"), and the Company shall (as applicable) cause the Board to promptly appoint such Linde Nominee to the Board or include such Linde Nominee in the Board's slate of nominees to the stockholders of the Company for election at the applicable meeting of stockholders.

(b) In the event that a Linde Director for any reason ceases to serve as a member of the Board, whether due to the death, disability, resignation, removal or disqualification of such Linde Director or for any other reason, Linde shall have the right, exercisable by written notice delivered to the Company referencing this Section 2.2, to designate a successor to fill such vacancy, and the Company shall cause the Board to promptly fill such vacancy with such successor designee, it being understood that any such designee shall serve the remainder of the term of the Linde Director whom such designee replaces.

(c)

(i) If any Linde Nominee is not appointed to the Board within fifteen (15) days of receipt by the Company of the written notice referred to in Section 2.2(a) or 2.2(b), as applicable (other than in the case of a notice delivered requesting the inclusion of the Linde Nominee in the Board's slate of nominees to the stockholders of the Company for election of directors at an annual or special meeting of stockholders), for any reason whatsoever, then in addition to all other remedies available to Linde hereunder, Linde shall have the right, exercisable by written notice delivered to the Company, to designate another Linde Nominee (and the provisions of this Section 2.2(c)(i) shall likewise apply to each such other Linde Nominee).

(ii) If any Linde Nominee designated by Linde for nomination to the Board pursuant to this Section 2.2 becomes incapable of serving on the Board as a result of such individual's death, withdrawal or disqualification prior to the applicable meeting of stockholders, Linde has the right, exercisable by written notice delivered to the Company, to designate another Linde Nominee to be included in the Board's slate of nominees to the stockholders of the Company for election at the applicable meeting of stockholders (and the provisions of this Section 2.2(c)(ii) shall likewise apply to each such other Linde Nominee).

(iii) In the event that the Linde Nominee included in the Board's slate of nominees to the stockholders of the Company for election of directors at an annual or special meeting of stockholders fails to be elected by the stockholders at such meeting for any reason whatsoever, the Company shall cause the Board to, as promptly as reasonably practicable, increase the size of the Board by one member and appoint the Linde Nominee to the Board in such newly-created vacancy. Any Linde Nominee appointed to the Board pursuant to the immediately preceding sentence shall be a director of the same class as the most recently elected class of directors.

(d) The Company shall:

(i) include the Linde Nominee in the Board's slate of nominees to the stockholders of the Company for each election of directors (or, if the Company then has a classified board of directors, for each election of directors of the class for which such Linde Nominee has been designated) and in the proxy statement prepared by management of the Company in connection with soliciting proxies for the meeting of the stockholders of the Company called with respect to the election of members of the Board (or the members of such class, as applicable), and at each adjournment or postponement thereof, and on each action or

approval by written consent of the Board or the stockholders of the Company with respect to the election or appointment of members of the Board (or the members of such class, as applicable);

(ii) recommend that the Company's stockholders vote in favor of the election of the Linde Nominee (along with the other individuals in the Board's slate of nominees) and solicit proxies in favor of such election and otherwise support the Linde Nominee for election in a manner no less favorable than the manner in which the Company supports other individuals in the Board's slate of nominees for election to the Board; and

(iii) not (x) make or recommend any amendment to the Certificate of Incorporation or the Company's bylaws that could reasonably be expected to have an adverse effect on the rights of any Linde Entity under this Section 2.2 or (y) take any other action for the purpose of adversely affecting the rights of the Linde Entities under this Section 2.2, in each case without the prior written approval of Linde.

(e) As a condition to the Linde Nominee's nomination for election as a director of the Company at any annual or special meeting of stockholders of the Company, Linde must provide to the Company, to the same extent as provided with respect to the Company's other nominees to the Board, such information as is required to be disclosed in proxy statements under applicable law or which is otherwise necessary for the inclusion of the Linde Nominee on the Board's slate of nominees for election as directors.

(f) For the avoidance of doubt, the delivery of any notice by Linde to the Company pursuant to this Section 2.2 shall not be subject to the provisions of Section 1.10 of the Company's bylaws or any other similar provisions that may from time to time be set forth in the Company's bylaws.

2.3 Subsidiary Boards; Committees. Except to the extent prohibited by applicable law or any applicable listing agreement to which the Company shall be a party, at the reasonable request of Linde exercisable by written notice delivered to the Company referencing this Section 2.3, the Linde Director shall be entitled to serve on the board of directors (or equivalent governing body) of each Subsidiary and on each committee of the Board or of the board of directors (or equivalent governing body) of each Subsidiary. Neither the Board nor any board of directors (or equivalent governing body) of any Subsidiary shall establish any committee without the prior written consent of Linde except to the extent required by law or any applicable listing agreement to which the Company shall be a party.

2.4 Compliance. The Linde Director shall, during the term of his or her service as a director of the Company, comply with the Company's code of conduct and all other company policies and guidelines applicable generally to directors serving on the Board which have been or are adopted by the Board.

2.5 Expense Reimbursement; Indemnification. The Company shall treat the Linde Director during the term of his or her service as a director of the Company consistent with its treatment of all other non-employee directors on the Board with respect to expense reimbursement and directors and officers liability insurance coverage. Promptly following the election or appointment of any Linde Nominee to the Board, the Company shall enter into an

indemnification agreement with such Linde Director in form and substance consistent with the indemnification agreements then in effect between the Company and the other members of the Board.

3. Miscellaneous.

3.1 Rules of Construction.

(a) An accounting term not otherwise defined herein has the meaning assigned to it in accordance with U.S. GAAP;

(b) References in the singular or to "him," "her," "it," "itself," or other like references, and references in the plural or the feminine or masculine or neutral reference, as the case may be, shall also, when the context so requires, be deemed to include the plural or singular, or the masculine or feminine or neutral reference, as the case may be;

(c) References to Sections shall refer to sections of this Agreement, unless otherwise specified;

(d) The headings in this Agreement are for convenience and identification only and are not intended to describe, interpret, define or limit the scope, extent or intent of this Agreement or any provision hereof;

(e) This Agreement shall be construed without regard to any presumption or other rule requiring construction against the party that drafted and caused this Agreement to be drafted;

(f) All monetary figures shall be in United States dollars unless otherwise specified, and any monetary figure in United States dollars shall be deemed to refer to the equivalent amount of foreign currency when used in a context which refers to or includes operations conducted principally outside of the United States;

(g) References to "include," "includes" and "including" in this Agreement shall be deemed to be followed by ", without limitation," whether or not so specified;

(h) The word "extent" in the phrase "to the extent" shall mean the degree to which a subject or other theory extends, and such phrase shall not mean "if;" and

(i) References to "ordinary course of business" in this Agreement shall mean "ordinary course of business consistent with past practice," whether or not so specified.

3.2 Further Actions. Each party hereto shall cooperate with each other party, shall do and perform or cause to be done and performed all further acts and things, and shall execute and deliver all other agreements, certificates, instruments and documents as any other party hereto reasonably may request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

3.3 Notices.

(a) Unless otherwise expressly provided herein, all notices, requests, demands, claims and other communications provided for under the provisions of this Agreement shall be in writing. Any notice, request, demand, claim or other communication hereunder shall be sent by (i) personal delivery (including receipted courier service) or overnight delivery service to the intended recipient at the address set forth below, (ii) facsimile or electronic mail, with confirmation of receipt, to the number or email address of the intended recipient set forth below (provided that a copy is also sent by another permitted method; and provided, further, that delivery to Linde may not be sent by facsimile), (iii) nationally recognized overnight delivery courier service to the intended recipient at the address set forth below, or (iv) registered or certified mail, return receipt requested, postage prepaid, to the intended recipient at the address set forth below:

(i) If to the Company, at the address indicated below, or at such other address as the Company may hereafter designate by written notice to Linde:

Bellerophon Therapeutics, Inc.
53 Frontage Road, Suite 301
Hampton, NJ 08827
Attn: Chief Executive Officer
Fax: 844-325-6587
Email: jon.peacock@bellerophon.com

with copies (which shall not constitute notice) to:

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attn: Lia Der Marderosian, Esq.
Fax: 617-526-5000
Email: lia.dermarderosian@wilmerhale.com

and

Cravath, Swaine & Moore LLP
825 Eighth Avenue
New York, NY 10019
Attn: Richard Hall, Esq.
Fax: 212-474-3700
Email: rhall@cravath.com

(ii) If to Linde, at the address set forth below, or at such other address as Linde may hereafter designate by written notice to the Company:

Linde North America, Inc.
575 Mountain Avenue

Murray Hill, NJ 07974
Attn: Jens Luehring
Email: Jens.Luehring@linde.com

with a copy (which shall not constitute notice) to:

Cravath, Swaine & Moore LLP
825 Eighth Avenue
New York, NY 10019
Attn: Richard Hall, Esq.
Fax: 212-474-3700
Email: rhall@cravath.com

(b) Notices shall be deemed to have been received:

(i) If given by personal delivery or by facsimile or electronic transmission, on the day given, if given before 5:00 PM local time on a business day in the jurisdiction of the intended recipient; otherwise on the next business day, provided that receipt of any facsimile or electronic transmission is confirmed by written evidence of delivery of facsimile, electronic confirmation of delivery or written acknowledgment of receipt thereof by the recipient;

(ii) If given by nationally recognized overnight delivery courier service, on the date of delivery indicated in the records of such courier service; and

(iii) If given by registered or certified mail, return receipt requested, postage prepaid, on the date of delivery indicated on the return receipt.

3.4 Governing Law. This Agreement shall in all respects be governed by, and construed in accordance with, the laws (excluding conflict of laws rules and principles) of the State of Delaware applicable to agreements made and to be performed entirely within such State, including all matters of construction, validity and performance.

3.5 Specific Performance. The parties agree that irreparable damage would occur in the event that any of the provisions of this Agreement were not performed in accordance with its specific terms or were otherwise breached and that money damages or other remedy at law would not be a sufficient or adequate remedy for any breach or violation of, or a default under, this Agreement. It is accordingly agreed that, notwithstanding anything to the contrary contained in this Agreement, each of the parties shall be entitled, without any requirement for the securing or posting of any bond with respect to such remedy, to an injunction or injunctions to prevent or restrain any breach, violation or default, or threatened breach, violation or default, of this Agreement and to enforce specifically the terms and provisions hereof exclusively in any state or federal court having jurisdiction, such remedy being in addition to any other remedy to which any party may be entitled at law or in equity.

3.6 Entire Agreement. This Agreement, including, to the extent referred to herein, the Certificate of Incorporation and the Voting Agreement, constitutes the entire

agreement of the parties relating to the subject matter hereof and supersedes all prior agreements and undertakings, whether oral or written. There are no representations, agreements, arrangements or understandings, oral or written, between or among the parties relating to the subject matter of this Agreement which are not fully expressed in this Agreement.

3.7 Severability. Should any provision of this Agreement or the application thereof to any Person or circumstance be held invalid or unenforceable to any extent, (a) such provision shall be ineffective to the extent, and only to the extent, of such invalidity or unenforceability and shall be enforced to the greatest extent permitted by law; (b) such invalidity or unenforceability with respect to any Person or in any jurisdiction shall not invalidate or render unenforceable such provision as applied (i) to any other Persons or circumstances or (ii) in any other jurisdiction; and (c) such invalidity or unenforceability shall not affect or invalidate any other provision of this Agreement.

3.8 Amendments and Waivers. This Agreement and any of the provisions hereof may be amended, modified or supplemented, in whole or in part, only by written agreement of the parties. The observance of any provision of this Agreement may be waived in writing by the party that will lose the benefit of such provision as a result of such waiver. The waiver by any party hereto of a breach by any party hereto of any provision of this Agreement shall not operate or be construed as a waiver of such breach by any other party hereto, except as otherwise explicitly provided for in the writing evidencing such waiver. Except as otherwise expressly provided herein, no failure on the part of any party to exercise, and no delay in exercising, any right, power or remedy hereunder, or otherwise available in respect hereof at law or in equity, shall operate as a waiver thereof, nor shall any single or partial exercise of such right, power or remedy by such party preclude any other or further exercise thereof or the exercise of any other right, power or remedy.

3.9 No Third Party Beneficiaries. Nothing in this Agreement, whether express or implied, shall be construed to give any Person (other than the parties hereto and their respective successors and permitted assigns who comply with the terms hereof and agree in writing to be bound by the provisions hereof) any legal or equitable right, remedy or claim under or in respect of this Agreement or any covenants, conditions or provisions contained herein, as a third party beneficiary or otherwise. Notwithstanding the foregoing, each Linde Director shall be a third party beneficiary of the provisions of Section 2.5 and shall be entitled to enforce such provisions directly.

3.10 Assignments. The provisions of this Agreement shall be binding upon and inure to the benefit of the Company and Linde and their respective successors and permitted assigns. This Agreement shall not be assignable by any of the parties hereto without the prior written consent of the other parties; provided, that Linde (i) may assign its rights and duties under this Agreement to any other Linde Entity at any time, (ii) at any time prior to the consummation of an Initial Public Offering, may assign its rights and duties under this Agreement to any Person who acquires shares of Common Stock from any of the Linde Entities and (iii) at any time following the consummation of an Initial Public Offering, may assign its rights and duties under this Agreement to a Person who acquires, in a transaction other than a Public Offering or a sale pursuant to Rule 144, at least fifty percent (50%) of the aggregate number of shares of Common Stock owned, directly or indirectly, by the Linde Entities as of

immediately prior to the consummation of such transaction (any Person described in the foregoing clauses (i) through (iii), an "**Assignee**"); provided, further, that no such assignment shall be binding upon or obligate the Company to any such Assignee unless and until such Assignee delivers to the Company (a) a written notice stating the name and address of such Assignee and identifying the shares of Common Stock owned by such Assignee and (b) a written instrument by which such Assignee agrees to be bound by the provisions of this Agreement applicable to the Linde Entities to the same extent as if such Assignee were a party hereto. Upon any assignment in accordance with this Section 3.10, the Assignee shall succeed to, and be substituted for, and may exercise every right and power of, the assigning Linde Entity under this Agreement.

3.11 Jurisdiction; Waiver of Jury Trial.

(a) Jurisdiction. Subject to Section 3.5, any action, suit or proceeding against any party to this Agreement arising out of or relating to this Agreement shall be brought in any federal or state court sitting in the Borough of Manhattan in the City of New York in the State of New York, and each of the parties hereby submits to the exclusive jurisdiction of such courts for the purpose of any such action, suit or proceeding. A final judgment in any such action, suit or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. To the extent that service of process by mail or by nationally recognized overnight delivery courier service is permitted by applicable law, each party irrevocably consents to the service of process in any such action, suit or proceeding in such courts by the mailing of such process by registered or certified mail, postage prepaid, return receipt request or by nationally recognized overnight delivery courier service to such party at its address for notices provided for in Section 3.3. Each party irrevocably waives and agrees not to assert (i) any objection which it may ever have to the laying of venue of any such action, suit or proceeding in any federal or state court located in New York County in the State of New York, and (ii) any claim that any such action, suit or proceeding brought in any such court has been brought in an inconvenient forum.

(b) Waiver of Jury Trial. EACH PARTY IRREVOCABLY WAIVES, TO THE EXTENT LAWFUL, AND AGREES NOT TO ASSERT ANY RIGHT TO TRIAL BY JURY IN ANY ACTION, SUIT OR PROCEEDING ARISING OUT OF RELATING TO THIS AGREEMENT AND AGREES THAT ANY OF THEM MAY FILE A COPY OF THIS PARAGRAPH WITH ANY COURT AS WRITTEN EVIDENCE OF THE KNOWING, VOLUNTARY AND BARGAINED-FOR AGREEMENT AMONG THE PARTIES IRREVOCABLY TO WAIVE ITS RIGHT TO TRIAL BY JURY IN ANY ACTION, SUIT OR PROCEEDING ARISING OUT OF RELATING TO THIS AGREEMENT.

3.12 Counterparts. This Agreement may be executed in any number of counterparts with the same effect as if all signatory parties had signed the same document. All counterparts shall be construed together and shall constitute one and the same instrument. A signature delivered by facsimile or electronic transmission shall be deemed to be an original signature for all purposes under this Agreement.

3.13 Adjustments. Wherever in this Agreement there is a reference to a specific number or percentage of shares of Common Stock, then upon the occurrence of any

subdivision, combination, stock split, reverse split, stock dividend or other recapitalization of the Company, the specific number or percentage of shares of Common Stock so referenced in this Agreement shall automatically be proportionally adjusted to reflect the effect on the outstanding Common Stock by such subdivision, combination, stock split, reverse split, stock dividend or other recapitalization.

3.14 Attorneys' Fees. In the event that any action, suit or proceeding is brought for the purpose of determining or enforcing the right of any party or parties hereunder, the party or parties prevailing in such action, suit or proceeding shall be entitled to recover from the other party or parties all reasonable costs and expenses incurred by the prevailing party or parties in connection with such action, suit or proceeding, including reasonable attorneys' fees.

[*Signature Page Follows*]

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

COMPANY:

BELLEROPHON THERAPEUTICS, INC.

By: /s/ Jonathan M. Peacock
Name: Jonathan M. Peacock
Title: President and Chief Executive Officer

LINDE:

LINDE NORTH AMERICA, INC.

By: /s/ Jens Luehring
Name: Jens Luehring
Title: Head of Finance, Americas

[Signature Page to Linde Stockholders Agreement]

Exhibit 4.3

STOCKHOLDERS AGREEMENT

This STOCKHOLDERS AGREEMENT, dated as of February 12, 2015, is made and entered into by and among Bellerophon Therapeutics, Inc., a Delaware corporation (formerly Bellerophon Therapeutics LLC, a Delaware limited liability company), New Mountain Partners II (AIV-A), L.P., a Delaware limited partnership ("**NMP-A**"), New Mountain Partners II (AIV-B), L.P., a Delaware limited partnership ("**NMP-B**"), New Mountain Affiliated Investors II, L.P., a Delaware limited partnership ("**NMAI**"), and Allegheny New Mountain Partners, L.P., a Delaware limited partnership ("**ANMP**"). Capitalized terms shall have the meanings assigned to them in Section 1.

WHEREAS, in anticipation of its public offering, Bellerophon Therapeutics LLC has been converted on the date hereof from a limited liability company into a corporation known as Bellerophon Therapeutics, Inc. (the "**Conversion**"); and

WHEREAS, in connection with the Conversion, the parties have agreed to enter into this Agreement to provide the parties with the rights and obligations set forth in this Agreement.

NOW, THEREFORE, in consideration of the premises and the mutual agreements contained herein, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto hereby agree as follows:

1. Defined Terms.

1.1 Definitions. For purposes of this Agreement, the following terms have the following meanings:

"**Affiliate**" means, (a) with respect to any Person, any other Person which, directly or indirectly, controls, is controlled by or is under common control with such Person, where "**control**" means the possession, directly or indirectly, of the power to direct the management and policies of such Person, whether through the ownership of voting securities, by contract or otherwise, and (b) with respect to any individual, also means the spouse or child of such individual.

"**Agreement**" means this Stockholders Agreement, as the same may be amended, restated, modified or supplemented from time to time.

"**Beneficially Own**" means beneficially own as determined under Rule 13d-3 promulgated under the Securities Exchange Act of 1934, as amended from time to time.

"**Board**" means the board of directors of the Company as it may be composed from time to time in accordance with the Certificate of Incorporation, the Company's bylaws (as in effect from time to time), this Agreement and the General Corporation Law of the State of Delaware (as in effect from time to time).

"**Certificate of Incorporation**" means the Certificate of Incorporation of the Company, as in effect from time to time.

"**Common Stock**" means any shares of common stock, par value $0.01 per share, of the Company, now or hereafter authorized to be issued, and any and all equity interests of any kind whatsoever of the Company which may be issued on or after the date hereof in respect of, in exchange for, or upon conversion of the Common Stock pursuant to a merger, consolidation, stock split, reverse split, stock dividend, recapitalization of the Company or otherwise.

"**Company**" means Bellerophon Therapeutics, Inc., a Delaware corporation, and shall, to the extent this Agreement survives, include any successor thereto by merger, consolidation, acquisition of substantially all the assets thereof, or otherwise, including any parent or subsidiary thereof that undertakes a Public Offering in lieu of the Company.

"**Convertible Securities**" means (a) any options or warrants to purchase or other rights to acquire Common Stock, (b) any securities by their terms convertible into, or exercisable or exchangeable for, Common Stock (directly or indirectly) and (c) any options or warrants to purchase or other rights to acquire any such convertible, exercisable or exchangeable securities.

"**Indebtedness**" means all liabilities, obligations and indebtedness of the Company and the Subsidiaries (a) for borrowed money (other than trade debt, trade accounts payable and any other accrued current liabilities or obligations incurred or arising in the ordinary course of business); (b) evidenced by a note, bond, debenture or similar instrument; (c) created or arising under any capital lease, conditional sale, earn out or other arrangement for the deferral of purchase price of any property; (d) under letters of credit, banker's acceptances or similar credit transactions; (e) for any other Person's obligation or indebtedness of the same type as any of the foregoing, whether as obligor, guarantor or otherwise; (f) for interest on any of the foregoing; and (g) for any premiums, prepayment or termination fees, expenses or breakage costs due upon prepayment of any of the foregoing.

"**Initial Public Offering**" means the first Public Offering.

"NMP Entities" means NMP-A, NMP-B, NMAI and ANMP and any Affiliate of any of the foregoing.

"**NMP Holder**" means any of the NMP Entities and any Person that acquires shares of Common Stock from any of the NMP Entities or other NMP Holders in a transaction other than a Public Offering or a sale pursuant to Rule 144.

"**Non-Voting Common Stock**" means any Common Stock designated as non-voting Common Stock when issued by the Company.

"**Person**" means any individual, corporation, association, partnership (general or limited), joint venture, trust, estate, limited liability company, organization or other legal entity, or any nation, government, governmental agency or political subdivision thereof, or any person or body exercising executive, legislative, judicial, regulatory, administrative or taxing functions of or pertaining to government, including any court.

"**Public Offering**" means a public offering of equity interests in the Company through a registration statement (other than a Form S-8 or successor forms) filed with, and declared effective by, the United States Securities and Exchange Commission and pursuant to

which such equity interests are authorized and approved for listing on a national securities exchange.

"**Rule 144**" means Rule 144 promulgated under the Securities Act of 1933, as amended from time to time.

"Section 2 Termination Date" means the first date after the consummation of an Initial Public Offering on which no NMP Holder, together with its Affiliates, Beneficially Owns (a) at least fifty percent (50%) of the sum of (i) the aggregate number of shares of Common Stock Beneficially Owned by the NMP Entities as of immediately prior to the consummation of the Initial Public Offering plus (ii) the aggregate number of shares of Common Stock, if any, acquired by any of the NMP Entities from the Company in connection with or subsequent to the consummation of the Initial Public Offering and (b) at least fifteen (15%) of the number of shares of Common Stock that were set forth as outstanding on the cover of the Company's then most recently filed Annual Report on Form 10-K or Quarterly Report on Form 10-Q, as the case may be; provided that the Section 2 Termination Date shall be deemed to have occurred in the event that: (A) an NMP Holder other than any NMP Entity, or any of their respective Affiliates, Beneficially Owns the percentage of shares described in clause (a) of this definition; (B) the rights described in Section 2.2 hereof have not been assigned to such NMP Holder pursuant to Section 4.10 hereof; and (C) the aggregate number of shares of Common Stock then Beneficially Owned by the NMP Entities constitutes less than fifteen percent (15%) of the sum of (x) the aggregate number of shares of Common Stock Beneficially Owned by the NMP Entities as of immediately prior to the consummation of the Initial Public Offering plus (y) the aggregate number of shares of Common Stock, if any, acquired by any of the NMP Entities from the Company in connection with or subsequent to the consummation of the Initial Public Offering.

"**Section 3.2 Termination Date**" means the first date after the consummation of an Initial Public Offering on which the aggregate number of shares of Common Stock then Beneficially Owned by the NMP Entities constitutes either (a) less than fifty percent (50%) of the sum of (i) the aggregate number of shares of Common Stock Beneficially Owned by the NMP Entities as of immediately prior to the consummation of the Initial Public Offering plus (ii) the aggregate number of shares of Common Stock, if any, acquired by any of the NMP Entities from the Company in connection with or subsequent to the consummation of the Initial Public Offering or (b) less than fifteen (15%) of the number of shares of Common Stock that were set forth as outstanding on the cover of the Company's then most recently filed Annual Report on Form 10-K or Quarterly Report on Form 10-Q, as the case may be.

"**Subsidiary**" means any direct or indirect subsidiary of the Company.

"**Voting Agreement**" means the Voting Agreement, dated as of February 12, 2014, by and among the Company and the stockholders party thereto from time to time, as the same may be amended, restated, modified or supplemented from time to time.

"**Voting Agreement NMP Director**" means any member of the Board who was designated by the NMP Entities pursuant to the Voting Agreement.

"**Voting Common Stock**" means any Common Stock designated as voting Common Stock when issued by the Company.

1.2 Other Defined Terms. The following is a list of the remaining defined terms used in this Agreement:

Term	Section
ANMP	Preamble
Assignee	4.10
Conversion	Recitals
NMAI	Preamble
NMP-A	Preamble
NMP-B	Preamble
NMP Director	2.2(a)
NMP Nominee	2.2(a)

2. Board of Directors.

2.1 Effectiveness and Termination. This Section 2 shall, without further action of any of the parties, (a) become effective concurrently with the termination of the Voting Agreement and (b) terminate automatically and be of no further force and effect at the close of business on the Section 2 Termination Date.

2.2 Director Nomination Rights.

(a) The NMP Entities shall have the right, at any time and from time to time, exercisable by written notice delivered to the Company referencing this Section 2.2, to designate one (1) individual to be appointed to the Board or nominated for election to the Board in each case pursuant to the procedures set forth in this Section 2.2 (each such individual designated by the NMP Entities pursuant to this Section 2.2, an "**NMP Nominee**", and any NMP Nominee who is appointed or elected to the Board pursuant to this Section 2.2, an "**NMP Director**"), and the Company shall (as applicable) cause the Board to promptly appoint such NMP Nominee to the Board or include such NMP Nominee in the Board's slate of nominees to the stockholders of the Company for election at the applicable meeting of stockholders.

(b) In the event that an NMP Director for any reason ceases to serve as a member of the Board, whether due to the death, disability, resignation, removal or disqualification of such NMP Director or for any other reason, the NMP Entities shall have the right, exercisable by written notice delivered to the Company referencing this Section 2.2, to designate a successor to fill such vacancy, and the Company shall cause the Board to promptly fill such vacancy with such successor designee, it being understood that any such designee shall serve the remainder of the term of the NMP Director whom such designee replaces.

(c)

(i) If any NMP Nominee is not appointed to the Board within fifteen (15) days of receipt by the Company of the written notice referred to in Section 2.2(a) or 2.2(b), as applicable (other than in the case of a notice delivered requesting the inclusion of the NMP Nominee in the Board's slate of nominees to the stockholders of the Company for election of directors at an annual or special meeting of stockholders), for any reason whatsoever, then in addition to all other remedies available to the NMP Entities hereunder, the NMP Entities shall have the right, exercisable by written notice delivered to the Company, to designate another NMP Nominee (and the provisions of this Section 2.2(c)(i) shall likewise apply to each such other NMP Nominee).

(ii) If any NMP Nominee designated by the NMP Entities for nomination to the Board pursuant to this Section 2.2 becomes incapable of serving on the Board as a result of such individual's death, withdrawal or disqualification prior to the applicable meeting of stockholders, the NMP Entities have the right, exercisable by written notice delivered to the Company, to designate another NMP Nominee to be included in the Board's slate of nominees to the stockholders of the Company for election at the applicable meeting of stockholders (and the provisions of this Section 2.2(c)(ii) shall likewise apply to each such other NMP Nominee).

(iii) In the event that the NMP Nominee included in the Board's slate of nominees to the stockholders of the Company for election of directors at an annual or special meeting of stockholders fails to be elected by the stockholders at such meeting for any reason whatsoever, the Company shall cause the Board to, as promptly as reasonably practicable, increase the size of the Board by one member and appoint the NMP Nominee to the Board in such newly-created vacancy. Any NMP Nominee appointed to the Board pursuant to the immediately preceding sentence shall be a director of the same class as the most recently elected class of directors.

(d) The Company shall:

(i) include the NMP Nominee in the Board's slate of nominees to the stockholders of the Company for each election of directors (or, if the Company then has a classified board of directors, for each election of directors of the class for which such NMP Nominee has been designated) and in the proxy statement prepared by management of the Company in connection with soliciting proxies for the meeting of the stockholders of the Company called with respect to the election of members of the Board (or the members of such class, as applicable), and at each adjournment or postponement thereof, and on each action or approval by written consent of the Board or the stockholders of the Company with respect to the election or appointment of members of the Board (or the members of such class, as applicable);

(ii) recommend that the Company's stockholders vote in favor of the election of the NMP Nominee (along with the other individuals in the Board's slate of nominees) and solicit proxies in favor of such election and otherwise support the NMP Nominee for election in a manner no less favorable than the manner in which the Company supports other individuals in the Board's slate of nominees for election to the Board; and

(iii) not (x) make or recommend any amendment to the Certificate of Incorporation or the Company's bylaws that could reasonably be expected to have an adverse effect on the rights of the NMP Entities under this Section 2.2 or (y) take any other action for the purpose of adversely affecting the rights of the NMP Entities under this Section 2.2, in each case without the prior written approval of the NMP Entities.

(e) As a condition to the NMP Nominee's nomination for election as a director of the Company at any annual or special meeting of stockholders of the Company, the NMP Entities must provide to the Company, to the same extent as provided with respect to the Company's other nominees to the Board, such information as is required to be disclosed in proxy statements under applicable law or which is otherwise necessary for the inclusion of the NMP Nominee on the Board's slate of nominees for election as directors.

(f) For the avoidance of doubt, the delivery of any notice by any NMP Entity to the Company pursuant to this Section 2.2 shall not be subject to the provisions of Section 1.10 of the Company's bylaws or any other similar provisions that may from time to time be set forth in the Company's bylaws.

2.3 Lead Director. The NMP Entities shall have the right, at any time and from time to time, exercisable by written notice delivered to the Company referencing this Section 2.3, to designate the Lead Director from among the members of the Board and to remove such Lead Director (and designate his or her replacement) from such role at any time, with or without cause, such Lead Director having such rights and obligations as set forth in the Company's Certificate of Incorporation and/or bylaws, as applicable.

2.4 Subsidiary Boards; Committees. Except to the extent prohibited by applicable law or any applicable listing agreement to which the Company shall be a party, at the reasonable request of the NMP Entities exercisable by written notice delivered to the Company referencing this Section 2.4, the NMP Director shall be entitled to serve on the board of directors (or equivalent governing body) of each Subsidiary and on each committee of the Board or of the board of directors (or equivalent governing body) of each Subsidiary. Neither the Board nor any board of directors (or equivalent governing body) of any Subsidiary shall establish any committee without the prior written consent of the NMP Entities except to the extent required by law or any applicable listing agreement to which the Company shall be a party.

2.5 Compliance. The NMP Director shall, during the term of his or her service as a director of the Company, comply with the Company's code of conduct and all other company policies and guidelines applicable generally to directors serving on the Board which have been or are adopted by the Board.

2.6 Expense Reimbursement; Indemnification. The Company shall treat the NMP Director during the term of his or her service as a director of the Company consistent with its treatment of all other non-employee directors on the Board with respect to expense reimbursement and directors and officers liability insurance coverage. Promptly following the election or appointment of any NMP Nominee to the Board, the Company shall enter into an indemnification agreement with such NMP Director in form and substance consistent with the

indemnification agreements then in effect between the Company and the other members of the Board.

3. Negative Covenants.

3.1 Prior to Initial Public Offering. In addition to any requirements imposed by the General Corporation Law of the State of Delaware and any agreement binding upon the Company, until the earlier of the consummation of an Initial Public Offering and the date on which the aggregate number of shares of Common Stock then Beneficially Owned by the NMP Holders constitutes less than fifteen (15%) of the number of shares of Common Stock Beneficially Owned by the NMP Holders as of the date hereof, the Company shall not, and shall cause each of the Subsidiaries not to, take any of the following actions without the prior written approval of the NMP Entities:

(a) consolidate or merge into or with any other Person, sell, lease or otherwise transfer all or a significant portion of its assets or equity interests or any business division to another Person, enter into any other similar business combination transaction with another Person, transfer the rights (including by way of grant of any license or sub-license) to all or a significant portion of its assets to another Person, or effect a liquidation, dissolution or winding-up (other than any such transaction entered into solely between the Company and one or more of its wholly owned Subsidiaries or between one or more wholly owned Subsidiaries);

(b) authorize, issue, sell, offer for sale or solicit offers to buy (by merger or otherwise) any shares of Common Stock or any Convertible Securities or any other equity or debt securities or rights to acquire any equity or debt securities of the Company or any of the Subsidiaries, other than (i) issuances of Non-Voting Common Stock upon the exercise of any options to purchase shares of Non-Voting Common Stock outstanding as of the date hereof, (ii) the granting of any rights pursuant to any equity incentive plan, the adoption of which plan received the approval of the Board (including the approval of at least one (1) Voting Agreement NMP Director) and the NMP Entities and which grants have received the approval of the Board (including the approval of at least one (1) Voting Agreement NMP Director) and the NMP Entities, or (iii) the issuance of any equity or debt securities by a wholly owned Subsidiary to the Company or to another wholly owned Subsidiary or the issuance of any debt securities by the Company to a wholly owned Subsidiary;

(c) incur, create, suffer to exist, issue, assume, guarantee or otherwise become directly or indirectly liable, contingently or otherwise, with respect to any Indebtedness, or refinance any Indebtedness, other than Indebtedness incurred by a wholly owned Subsidiary to the Company or to another wholly owned Subsidiary or by the Company to a wholly owned Subsidiary;

(d) effect any stock dividend, stock split or other subdivision or combination of Common Stock or other equity interests of the Company or other recapitalization of the Company;

(e) effect any redemption, retirement, purchase or other acquisition, directly or indirectly, of any Common Stock or other equity interests of the

Company, other than the repurchase of Common Stock from employees, officers, directors or consultants of or other persons performing services for the Company or any Subsidiary pursuant to agreements under which the Company has the option to repurchase such Common Stock upon the occurrence of certain events, such as the termination of employment, or through the exercise of any right of first refusal, which repurchase does not exceed $100,000 in any one instance or $250,000 in the aggregate in any fiscal year;

(f) effect an Initial Public Offering or, subject to the rights of any stockholder of the Company under the Registration Rights Agreement, dated as of February 12, 2015, by and among the Company and the stockholders party thereto from time to time, as the same may be amended, restated, modified or supplemented from time to time, a public offering of any securities of the Company;

(g) hire or replace any of the Company's Chief Executive Officer, Chief Financial Officer or next two (2) most senior executives (as determined by the Board), or materially amend the level or form of compensation or benefits payable to, or other compensation arrangements of, any such officer;

(h) acquire any assets other than in the ordinary course of business, including acquiring any ownership interest in any other Person, or acquire assets in the ordinary course of business in excess of $500,000 for the Company and the Subsidiaries in the aggregate in any fiscal year;

(i) adopt any annual budget or annual business plan or materially amend any such budget or business plan if adopted;

(j) declare or pay any dividend or distribution (other than dividends from a wholly owned Subsidiary to its parent company);

(k) authorize or amend any employee option or incentive plan;

(l) amend, repeal or change (whether by merger or otherwise) any of the provisions of the Certificate of Incorporation or the bylaws of the Company; or

(m) agree or otherwise commit to take any of the actions set forth in any of clauses (a) through (l) of this Section 3.1 (unless such agreement or commitment is expressly conditioned on obtaining the prior approval set forth in this Section 3.1).

3.2 Following Initial Public Offering. In addition to any requirements imposed by the General Corporation Law of the State of Delaware and any agreement binding upon the Company, from and after the consummation of an Initial Public Offering and until the close of business on the Section 3.2 Termination Date, the Company shall not, and shall cause each of the Subsidiaries not to, take any of the following actions without the prior written approval of the NMP Entities:

(a) consolidate or merge into or with any other Person, sell, lease or otherwise transfer all or a significant portion of its assets or equity interests or any business division to another Person, enter into any other similar business combination transaction

with another Person, transfer the rights (including by way of grant of any license or sub-license) to all or a significant portion of its assets to another Person, or effect a liquidation, dissolution or winding-up (other than any such transaction entered into solely between the Company and one or more of its wholly owned Subsidiaries or between one or more wholly owned Subsidiaries);

(b) authorize, issue, sell, offer for sale or solicit offers to buy (by merger or otherwise) any shares of Common Stock or any Convertible Securities or any other equity or debt securities or rights to acquire any equity or debt securities of the Company or any of the Subsidiaries, other than (i) issuances of Common Stock upon the exercise of any options to purchase shares of Common Stock outstanding immediately following the Initial Public Offering, (ii) the granting of any rights pursuant to any equity incentive plan, the adoption of which plan received the approval of the Board and the NMP Entities and which grants have received the approval of the Board and the NMP Entities, or (iii) the issuance of any equity or debt securities by a wholly owned Subsidiary to the Company or to another wholly owned Subsidiary or the issuance of any debt securities by the Company to a wholly owned Subsidiary;

(c) incur, create, suffer to exist, issue, assume, guarantee or otherwise become directly or indirectly liable, contingently or otherwise, with respect to, or refinance, any Indebtedness (other than (i) Indebtedness described in clause (c) of the definition thereof, (ii) Indebtedness described in clauses (f) and (g) of the definition thereof to the extent such obligations are not capitalized to principal, and (iii) trade debt, trade accounts payable and any other accrued current liabilities or obligations incurred or arising in the ordinary course of business) in an aggregate principal amount in excess of $5,000,000, other than any such Indebtedness incurred by a wholly owned Subsidiary to the Company or to another wholly owned Subsidiary or by the Company to a wholly owned Subsidiary;

(d) hire or replace the Company's Chief Executive Officer; or

(e) agree or otherwise commit to take any of the actions set forth in any of clauses (a) through (d) of this Section 3.2 (unless such agreement or commitment is expressly conditioned on obtaining the prior approval set forth in this Section 3.2).

3.3 Termination. The provisions of Section 3.2 shall, without further action of any of the parties, terminate automatically and shall be of no further force and effect at the close of business on the Section 3.2 Termination Date.

4. Miscellaneous.

4.1 Rules of Construction.

(a) An accounting term not otherwise defined herein has the meaning assigned to it in accordance with U.S. GAAP;

(b) References in the singular or to "him," "her," "it," "itself," or other like references, and references in the plural or the feminine or masculine or neutral reference, as the case may be, shall also, when the context so requires, be deemed to include the plural or singular, or the masculine or feminine or neutral reference, as the case may be;

(c) References to Sections shall refer to sections of this Agreement, unless otherwise specified;

(d) The headings in this Agreement are for convenience and identification only and are not intended to describe, interpret, define or limit the scope, extent or intent of this Agreement or any provision hereof;

(e) This Agreement shall be construed without regard to any presumption or other rule requiring construction against the party that drafted and caused this Agreement to be drafted;

(f) All monetary figures shall be in United States dollars unless otherwise specified, and any monetary figure in United States dollars shall be deemed to refer to the equivalent amount of foreign currency when used in a context which refers to or includes operations conducted principally outside of the United States;

(g) References to "include," "includes" and "including" in this Agreement shall be deemed to be followed by ", without limitation," whether or not so specified;

(h) The word "extent" in the phrase "to the extent" shall mean the degree to which a subject or other theory extends, and such phrase shall not mean "if;" and

(i) References to "ordinary course of business" in this Agreement shall mean "ordinary course of business consistent with past practice," whether or not so specified.

4.2 Further Actions. Each party hereto shall cooperate with each other party, shall do and perform or cause to be done and performed all further acts and things, and shall execute and deliver all other agreements, certificates, instruments and documents as any other party hereto reasonably may request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

4.3 Notices.

(a) Unless otherwise expressly provided herein, all notices, requests, demands, claims and other communications provided for under the provisions of this Agreement shall be in writing. Any notice, request, demand, claim or other communication hereunder shall be sent by (i) personal delivery (including receipted courier service) or overnight delivery service to the intended recipient at the address set forth below, (ii) facsimile or electronic mail, with confirmation of receipt, to the number or email address of the intended recipient set forth below (provided that a copy is also sent by another permitted method; and provided, further, that delivery to the NMP Entities may not be sent by facsimile), (iii) nationally recognized overnight delivery courier service to the intended recipient at the address set forth below, or (iv) registered or certified mail, return receipt requested, postage prepaid, to the intended recipient at the address set forth below:

(i) If to the Company, at the address indicated below, or at such other address as the Company may hereafter designate by written notice to the NMP Entities:

Bellerophon Therapeutics, Inc.
53 Frontage Road, Suite 301
Hampton, NJ 08827
Attn: Chief Executive Officer
Fax: 844-325-6587
Email: jon.peacock@bellerophon.com

with copies (which shall not constitute notice) to:

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attn: Lia Der Marderosian, Esq.
Fax: 617-526-5000
Email: lia.dermarderosian@wilmerhale.com

and

Fried, Frank, Harris, Shriver & Jacobson LLP
One New York Plaza
New York, NY 10004
Attn: Aviva F. Diamant, Esq. and Abigail P. Bomba, Esq.
Fax: 212-859-4000
Email: aviva.diamant@friedfrank.com and
abigail.bomba@friedfrank.com

(ii) If to the NMP Entities, at the address set forth below, or at such other address as the NMP Entities may hereafter designate by written notice to the Company:

c/o New Mountain Capital, L.L.C.
787 Seventh Avenue, 49th Floor
New York, NY 10019
Attn: Matthew Holt
Email: mholt@newmountaincapital.com

with a copy (which shall not constitute notice) to:

Fried, Frank, Harris, Shriver & Jacobson LLP
One New York Plaza
New York, NY 10004
Attn: Aviva F. Diamant, Esq. and Abigail P. Bomba, Esq.
Fax: 212-859-4000
Email: aviva.diamant@friedfrank.com and
abigail.bomba@friedfrank.com

(b) Notices shall be deemed to have been received:

(i) If given by personal delivery or by facsimile or electronic transmission, on the day given, if given before 5:00 PM local time on a business day in the jurisdiction of the intended recipient; otherwise on the next business day, provided that receipt of any facsimile or electronic transmission is confirmed by written evidence of delivery of facsimile, electronic confirmation of delivery or written acknowledgment of receipt thereof by the recipient;

(ii) If given by nationally recognized overnight delivery courier service, on the date of delivery indicated in the records of such courier service; and

(iii) If given by registered or certified mail, return receipt requested, postage prepaid, on the date of delivery indicated on the return receipt.

4.4 Governing Law. This Agreement shall in all respects be governed by, and construed in accordance with, the laws (excluding conflict of laws rules and principles) of the State of Delaware applicable to agreements made and to be performed entirely within such State, including all matters of construction, validity and performance.

4.5 Specific Performance. The parties agree that irreparable damage would occur in the event that any of the provisions of this Agreement were not performed in accordance with its specific terms or were otherwise breached and that money damages or other remedy at law would not be a sufficient or adequate remedy for any breach or violation of, or a default under, this Agreement. It is accordingly agreed that, notwithstanding anything to the contrary contained in this Agreement, each of the parties shall be entitled, without any requirement for the securing or posting of any bond with respect to such remedy, to an injunction or injunctions to prevent or restrain any breach, violation or default, or threatened breach, violation or default, of this Agreement and to enforce specifically the terms and provisions hereof exclusively in any state or federal court having jurisdiction, such remedy being in addition to any other remedy to which any party may be entitled at law or in equity.

4.6 Entire Agreement. This Agreement, including, to the extent referred to herein, the Certificate of Incorporation, the Registration Rights Agreement and the Voting Agreement, constitutes the entire agreement of the parties relating to the subject matter hereof and supersedes all prior agreements and undertakings, whether oral or written. There are no representations, agreements, arrangements or understandings, oral or written, between or among the parties relating to the subject matter of this Agreement which are not fully expressed in this Agreement.

4.7 Severability. Should any provision of this Agreement or the application thereof to any Person or circumstance be held invalid or unenforceable to any extent, (a) such provision shall be ineffective to the extent, and only to the extent, of such invalidity or unenforceability and shall be enforced to the greatest extent permitted by law; (b) such invalidity or unenforceability with respect to any Person or in any jurisdiction shall not invalidate or render unenforceable such provision as applied (i) to any other Persons or circumstances or (ii) in any

other jurisdiction; and (c) such invalidity or unenforceability shall not affect or invalidate any other provision of this Agreement.

4.8 Amendments and Waivers. This Agreement and any of the provisions hereof may be amended, modified or supplemented, in whole or in part, only by written agreement of the parties. The observance of any provision of this Agreement may be waived in writing by the party that will lose the benefit of such provision as a result of such waiver. The waiver by any party hereto of a breach by any party hereto of any provision of this Agreement shall not operate or be construed as a waiver of such breach by any other party hereto, except as otherwise explicitly provided for in the writing evidencing such waiver. Except as otherwise expressly provided herein, no failure on the part of any party to exercise, and no delay in exercising, any right, power or remedy hereunder, or otherwise available in respect hereof at law or in equity, shall operate as a waiver thereof, nor shall any single or partial exercise of such right, power or remedy by such party preclude any other or further exercise thereof or the exercise of any other right, power or remedy.

4.9 No Third Party Beneficiaries. Nothing in this Agreement, whether express or implied, shall be construed to give any Person (other than the parties hereto and their respective successors and permitted assigns who comply with the terms hereof and agree in writing to be bound by the provisions hereof) any legal or equitable right, remedy or claim under or in respect of this Agreement or any covenants, conditions or provisions contained herein, as a third party beneficiary or otherwise. Notwithstanding the foregoing, each NMP Director shall be a third party beneficiary of the provisions of Section 2.6 and shall be entitled to enforce such provisions directly.

4.10 Assignments. The provisions of this Agreement shall be binding upon and inure to the benefit of the Company and the NMP Entities and their respective successors and permitted assigns. This Agreement shall not be assignable by any of the parties hereto without the prior written consent of the other parties; provided, that any of the NMP Entities (i) may assign its rights and duties under this Agreement to any other NMP Entity at any time, (ii) at any time prior to the consummation of an Initial Public Offering, may assign its rights and duties under this Agreement to any Person who acquires shares of Common Stock from any of the NMP Entities and (iii) at any time following the consummation of an Initial Public Offering, may assign its rights and duties under this Agreement (other than Section 3.2) to a Person who acquires, in a transaction other than a Public Offering or a sale pursuant to Rule 144, at least fifty percent (50%) of the aggregate number of shares of Common Stock owned, directly or indirectly, by the NMP Entities as of immediately prior to the consummation of such transaction (any Person described in the foregoing clauses (i) through (iii), an "**Assignee**"); provided, further, that no such assignment shall be binding upon or obligate the Company to any such Assignee unless and until such Assignee delivers to the Company (a) a written notice stating the name and address of such Assignee and identifying the shares of Common Stock owned by such Assignee and (b) a written instrument by which such Assignee agrees to be bound by the provisions of this Agreement applicable to the NMP Entities to the same extent as if such Assignee were a party hereto. Upon any assignment in accordance with this Section 4.10, the Assignee shall succeed to, and be substituted for, and may exercise every right and power of, the assigning NMP Entity under this Agreement; provided, that no rights or duties of the NMP Entities under Section 3.2 of this Agreement shall be assignable or delegable to any Person other than to an NMP Entity.

4.11 Jurisdiction; Waiver of Jury Trial.

(a) Jurisdiction. Subject to Section 4.5, any action, suit or proceeding against any party to this Agreement arising out of or relating to this Agreement shall be brought in any federal or state court sitting in the Borough of Manhattan in the City of New York in the State of New York, and each of the parties hereby submits to the exclusive jurisdiction of such courts for the purpose of any such action, suit or proceeding. A final judgment in any such action, suit or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. To the extent that service of process by mail or by nationally recognized overnight delivery courier service is permitted by applicable law, each party irrevocably consents to the service of process in any such action, suit or proceeding in such courts by the mailing of such process by registered or certified mail, postage prepaid, return receipt request or by nationally recognized overnight delivery courier service to such party at its address for notices provided for in Section 4.3. Each party irrevocably waives and agrees not to assert (i) any objection which it may ever have to the laying of venue of any such action, suit or proceeding in any federal or state court located in New York County in the State of New York, and (ii) any claim that any such action, suit or proceeding brought in any such court has been brought in an inconvenient forum.

(b) Waiver of Jury Trial. EACH PARTY IRREVOCABLY WAIVES, TO THE EXTENT LAWFUL, AND AGREES NOT TO ASSERT ANY RIGHT TO TRIAL BY JURY IN ANY ACTION, SUIT OR PROCEEDING ARISING OUT OF RELATING TO THIS AGREEMENT AND AGREES THAT ANY OF THEM MAY FILE A COPY OF THIS PARAGRAPH WITH ANY COURT AS WRITTEN EVIDENCE OF THE KNOWING, VOLUNTARY AND BARGAINED-FOR AGREEMENT AMONG THE PARTIES IRREVOCABLY TO WAIVE ITS RIGHT TO TRIAL BY JURY IN ANY ACTION, SUIT OR PROCEEDING ARISING OUT OF RELATING TO THIS AGREEMENT.

4.12 Counterparts. This Agreement may be executed in any number of counterparts with the same effect as if all signatory parties had signed the same document. All counterparts shall be construed together and shall constitute one and the same instrument. A signature delivered by facsimile or electronic transmission shall be deemed to be an original signature for all purposes under this Agreement.

4.13 Adjustments. Wherever in this Agreement there is a reference to a specific number or percentage of shares of Common Stock, then upon the occurrence of any subdivision, combination, stock split, reverse split, stock dividend or other recapitalization of the Company, the specific number or percentage of shares of Common Stock so referenced in this Agreement shall automatically be proportionally adjusted to reflect the effect on the outstanding Common Stock by such subdivision, combination, stock split, reverse split, stock dividend or other recapitalization.

4.14 Attorneys' Fees. In the event that any action, suit or proceeding is brought for the purpose of determining or enforcing the right of any party or parties hereunder, the party or parties prevailing in such action, suit or proceeding shall be entitled to recover from the other party or parties all reasonable costs and expenses incurred by the prevailing party or parties in connection with such action, suit or proceeding, including reasonable attorneys' fees.

[*Signature Page Follows*]

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

COMPANY:

BELLEROPHON THERAPEUTICS, INC.

By: /s/ Jonathan M. Peacock
Name: Jonathan M. Peacock
Title: President and Chief Executive Officer

[Signature Page to Stockholders Agreement (New Mountain)]

NMP ENTITIES:

NEW MOUNTAIN PARTNERS II (AIV-A), L.P.

By: New Mountain Investments II, L.L.C.
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

NEW MOUNTAIN PARTNERS II (AIV-B), L.P.

By: New Mountain Investments II, L.L.C.
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

NEW MOUNTAIN AFFILIATED INVESTORS II, L.P.

By: New Mountain Investments II, L.L.C.,
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

ALLEGHENY NEW MOUNTAIN PARTNERS, L.P.

By: New Mountain Investments II, L.L.C.,
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

Exhibit 10.8

EXECUTION VERSION

Confidential Materials omitted and filed separately with the
Securities and Exchange Commission. Double asterisks denote omissions.

AMENDED AND RESTATED

LICENSE AND COMMERCIALIZATION AGREEMENT

BY AND AMONG

IKARIA DEVELOPMENT SUBSIDIARY ONE LLC

AND

BIOLINERX LTD.

AND

BIOLINE INNOVATIONS JERUSALEM L.P.

AUGUST 26, 2009

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AMENDED AND RESTATED
LICENSE AND COMMERCIALIZATION AGREEMENT

This Amended and Restated License and Commercialization Agreement (the "Agreement") is entered into this 26th day of August, 2009, by and among **Ikaria Development Subsidiary One LLC**, a Delaware limited liability company having a principal place of business at 6 State Route 173, Clinton, NJ 08809, USA ("Ikaria"), **BioLineRx Ltd.**, a corporation organized and existing under the laws of the State of Israel and having a principal place of business at 19 Hartum Street, P.O. Box 45158, Jerusalem 91450, Israel ("BioLineRx Ltd."), and **BioLine Innovations Jerusalem L.P.**, a limited partnership organized and existing under the laws of the State of Israel and having a principal place of business at 19 Hartum Street, P.O. Box 45158, Jerusalem 91450, Israel ("BioLine Innovations"; together with BioLineRx Ltd., "BioLineRx").

INTRODUCTION

WHEREAS, BioLineRx owns or controls certain intellectual property rights covering a liquid polymer composed of Sodium Alginate and Ca-D-Gluconate (designated by BioLineRx as "BL-1040");

WHEREAS, BioLineRx is currently developing the Product (as defined below) as a medical device for the direct treatment of cardiac tissue following acute myocardial infarction;

WHEREAS, BioLineRx is concluding the safety and clinical trials of the Product that were initiated by BioLineRx prior to the Effective Date (as defined below);

WHEREAS, BioLineRx desires to grant to Ikaria the worldwide exclusive rights to Develop, Manufacture, and Commercialize Products (as such capitalized terms are defined below); and

WHEREAS, Ikaria desires to obtain such exclusive rights in accordance with the terms and conditions of this Agreement.

NOW, THEREFORE, BioLineRx and Ikaria agree as follows:

Article I
Definitions; Interpretation

When used in this Agreement, each of the following capitalized terms has the meaning set forth in this Article I:

Section 1.1 "Affiliate" shall mean, with respect to a Party, any Person that controls, is controlled by, or is under common control with such Party. For purposes of this Section 1.1, "control" shall refer to (a) in the case of a Person that is a corporate entity, direct or indirect ownership of more than fifty percent (50%) of the stock, shares or membership units having the right to vote for the election of a majority of the directors of such Person, and (b) in the case of a Person that is an entity, but is not a corporate entity, the possession, directly or indirectly, of the

power to direct, or cause the direction of, the management or policies of such Person, whether through the ownership of voting securities, by contract or otherwise.

Section 1.2 "BGN License Agreement" shall mean that certain License Agreement, dated January 10, 2005, as amended, by and among BioLine Jerusalem L.P. and B.G. Negev Technologies and Applications Ltd. ("BGN") on behalf of Ben Gurion University.

Section 1.3 "BioLineRx Know-How" shall mean all Know-How that is (a) necessary or useful for the Development, Manufacture, or Commercialization of any Product and (b) either (i) is Controlled by BioLineRx as of the Effective Date or (ii) BioLineRx comes to Control during the term of this Agreement.

Section 1.4 "BioLineRx Patent Rights" shall mean Patent Rights that claim or disclose BioLineRx Know-How, including the Patent Rights listed in Exhibit B.

Section 1.5 "BioLineRx Intellectual Property" shall mean BioLineRx Patent Rights (including Patent Rights in the Sublicensed IP), and BioLineRx Know-How (including Know-How in the Sublicensed IP).

Section 1.6 "Business Day" shall mean a day that is not a Saturday, a Sunday or a day on which banking institutions in New York, New York, USA are authorized by law to remain closed.

Section 1.7 "Commercialization" or "Commercialize" shall mean any activities directed to marketing, promoting, distributing, importing, exporting, or selling a product.

Section 1.8 "Commercially Reasonable Efforts" shall mean the efforts, expertise and resources normally used by a Party to Develop, Manufacture and Commercialize a product owned by it or to which it has rights, which is of similar market potential at a similar stage in its development or product life, taking into account issues of safety and efficacy, product profile, difficulty in developing the product, competitiveness of the marketplace for the product, the proprietary position of the product, the regulatory structure involved, the availability and level of reimbursement for such treatment by Third Party payors or health insurance plans, the potential total profitability of the applicable product(s) marketed or to be marketed and other relevant factors affecting the cost, risk and timing of Development and the total potential reward to be obtained if a product is Commercialized. The Parties agree that Commercially Reasonable Efforts shall require a Party to expend efforts, expertise and resources that such Party would normally expend to Develop, use, Manufacture and Commercialize a product owned by it or to which it has rights, taking into account the foregoing factors.

Section 1.9 "Confidential Information" shall mean, with respect to a disclosing Party, all Know-How or other information (whether or not patentable) regarding such Party's technology, products, business information or objectives (whether disclosed before or after the Effective Date) that is of a confidential and proprietary nature, including reports and audits under Section 4.3, the Development Plan, the Commercialization Plan, the terms of this Agreement, and all proprietary tangible materials (and data and information associated therewith) of such Party. Notwithstanding the foregoing, Confidential Information shall not include Know-How or other information that:

(a) was rightfully known or used by the receiving Party or its Affiliates without an obligation of confidentiality prior to its date of disclosure to the receiving Party as demonstrated by contemporaneous written records; or

(b) either before or after the date of the disclosure to the receiving Party is lawfully disclosed to the receiving Party or its Affiliates by sources other than the disclosing Party rightfully in possession of such information and not bound by confidentiality obligations to the disclosing Party; or

(c) either before or after the date of the disclosure to the receiving Party or its Affiliates is or becomes published or otherwise is or becomes part of the public domain through no breach hereof on the part of the receiving Party or its Affiliates; or

(d) is independently developed by or for the receiving Party or its Affiliates without reference to or use of the Confidential Information of the disclosing Party as demonstrated by contemporaneous written records.

Section 1.10 "Control" shall mean the legal authority or right of a Party or its Affiliates to grant a license or sublicense of intellectual property rights to the other Party, or to provide tangible material to or otherwise disclose proprietary or trade secret information to such other Party, without breaching the terms of any agreement with a Third Party. For the avoidance of doubt, BioLineRx Controls the Sublicensed IP.

Section 1.11 "Cover" or "Covered" shall mean, with respect to a Patent Right and a product, that, in the absence of ownership of (with a retained right to exploit), or a license granted under, a Valid Claim included in such Patent Right, the Manufacture, Development, Commercialization, use, sale, import, or offer for sale, as applicable, of such product would infringe such Valid Claim in the country where such activity occurs.

Section 1.12 "Development" or "Develop" shall mean development activities, including test method development and stability testing, toxicology, formulation, optimization, quality assurance/quality control development, statistical analysis, clinical studies, regulatory affairs, product approval, and registration.

Section 1.13 "Development Term" shall mean the term of development of Products by Ikaria.

Section 1.14 "EU" shall mean the European Union and all the member states thereof, as it may be comprised from time to time.

Section 1.15 "EU Milestone Conditions" shall mean (a) satisfaction of all requirements for [**], (b) [**] set forth therein, **and** (c) [**].

Section 1.16 "Executive Officers" shall mean the Chief Executive Officer of Ikaria (or a senior executive officer of Ikaria designated by Ikaria) and the Chief Executive Officer of BioLineRx (or a senior executive officer of BioLineRx designated by BioLineRx).

Section 1.17 "FDA" shall mean the United States Food and Drug Administration or any successor agency thereof.

Section 1.18 "Field" shall mean any and all uses described or claimed in the BioLineRx Patent Rights.

Section 1.19 "First Commercial Sale" shall mean, with respect to a Product in a country, the first commercial sale of such Product by Ikaria, its Affiliates, distributors, agents or Licensees in such country. Sales for clinical trial purposes or compassionate or similar use shall not be considered to constitute a First Commercial Sale.

Section 1.20 Intentionally Omitted

Section 1.21 Intentionally Omitted

Section 1.22 Intentionally Omitted

Section 1.23 Intentionally Omitted.

Section 1.24 Intentionally Omitted."

Section 1.25 "Know-How" shall mean any tangible or intangible know-how, expertise, information, inventions, discoveries, documents and other works of authorship, copyrights, trade secrets, data, or materials, whether proprietary or not, including ideas, concepts, formulas, methods, procedures, designs, technologies, compositions, plans, applications, technical data, data generated in clinical trials, samples, chemical compounds and biological materials and all derivatives, modifications and improvements thereof.

Section 1.26 "Knowledge" shall mean, with respect to a Party, the Party's actual knowledge together with any knowledge of any of the Party's officers or director-level employees, that a Person in such party's position would be expected to obtain given the exercise of reasonably prudent scientific and business diligence in accordance with the standards of companies of such Party's size in such Party's industry.

Section 1.27 "Licensee" shall mean any Person to whom Ikaria licenses its rights under this Agreement in the manner provided in Section 2.1, including any Third Party contractors.

Section 1.28 "Manufacturing" or "Manufacture" shall mean any activities associated with the production, manufacture, supply, processing, filling, packaging, labeling, shipping, or storage of a product or any components thereof, including process and formulation development, process validation, stability testing, manufacturing scale-up, development and commercial manufacture and analytical development, product characterization, quality assurance and quality control development, testing, and release.

Section 1.29 "Net Sales" shall mean, with respect to a Product, the gross amounts billed by Ikaria, its Affiliates, or Licensees in respect of sales of such Product by Ikaria and its Affiliates or Licensees to unrelated Third Parties, in each case less the following deductions:

(a) Trade, cash, or quantity discounts (including amounts incurred in connection with government mandated rebate programs) actually allowed and taken with respect to such sales;

(b) Tariffs, duties, excises, sales taxes or other taxes imposed upon and paid with respect to the production, sale, delivery, or use of the Product (excluding national, state, or local taxes based on income);

(c) Amounts repaid or credited by reason of billing corrections, rejections, defects, recalls, or returns (due to spoilage, damage, expiration of useful life or otherwise) or because of chargebacks, refunds or retroactive price reductions and allowances for wastage replacement and bad debts;

(d) Portions of invoices sales amounts included in Net Sales in prior periods that are actually written off by Ikaria, its Affiliates, or licenses as uncollectible; and

(e) Postage, freight, shipping, insurance, and other transportation related charges incurred in shipping a Product to Third Parties.

Such amounts shall be determined from the books and records of Ikaria, its Affiliates, or Licensees, maintained in accordance with generally accepted accounting principles, consistently applied. For the avoidance of doubt, in no event will fines, penalties or other monetary damages assessed against Ikaria, its Affiliates or Licensees by any governmental authority for violation of any applicable law, result in an appropriate deduction to Net Sales.

If one or more Products is sold as part of a Combination Product (as defined below), the Net Sales from the Combination Product, for the purposes of determining royalty payments, shall be determined by multiplying the Net Sales (as determined above) of the Combination Product, during the applicable royalty reporting period, by the fraction, A/(A+B), where A is the average sale price of the Product(s) when sold separately in finished form and B is the average sale price of the other components included in the Combination Product when sold separately in finished form, in each case in the applicable country during the applicable royalty reporting period or, if sales of both the Product(s) and the other components did not occur in such country in such period, then in the most recent royalty reporting period in which sales of both occurred. If such average sale price cannot be determined for both the Product(s) and all other components included in such Combination Product, Net Sales for the purposes of determining royalty payments shall be calculated by multiplying the Net Sales of the Combination Product by the fraction of C/(C+D) where C is the fair market value of the Product(s) and D is the fair market value of all other components included in the Combination Product. In such event, the Parties shall negotiate in good faith to arrive at a determination of the respective fair market values of the Product(s) and all other components included in the Combination Product. If the Parties are unable to agree on such determination within sixty (60) days, then such matter shall be resolved as provided in Article IX.

As used above, the term "Combination Product" means any therapeutic medical product that includes both (i) one or more Product(s) and (ii) other component(s).

Section 1.30 "On-Going Phase I/II Trial" shall mean that certain clinical trial of a Product that was initiated by BioLineRx prior to and that is ongoing as of the Effective Date, the protocol for which is attached hereto as Schedule 1.30.

Section 1.31 "Other On-Going Trials" shall mean those pre-clinical and CMC trials (other than the On-Going Phase I/II Trial) that were initiated by BioLineRx prior to, and that are ongoing as of, the Effective Date, descriptions of which are attached hereto as Schedule 1.31.

Section 1.32 "Party" shall mean BioLineRx or Ikaria; "Parties" shall mean BioLineRx and Ikaria.

Section 1.33 "Patent Rights" shall mean United States and foreign patents and patent applications (including provisional applications) and all substitutions, divisionals, continuations, continuations-in-part, reissuances, reexaminations, registrations, renewals, confirmations, supplementary protection certificates and extensions thereof.

Section 1.34 "Person" shall mean any natural person or any corporation, company, partnership, joint venture, firm, university, other entity, governmental authority, or subdivision thereof.

Section 1.35 "Pivotal Clinical Trial" shall mean a randomized, controlled clinical trial of a Product designed to demonstrate statistically significant clinical efficacy and safety in human patients (in conjunction with performance of a therapeutic procedure) pursuant to a clinical study agreed with the FDA, which trial the FDA accepts as a pivotal clinical trial necessary for Regulatory Approval of such Product. An outline of the structure of the initial Pivotal Clinical Trial is attached as Schedule 1.35.

Section 1.36 "Primary Indication" shall mean the diagnosis, prevention, mitigation, or treatment of injury to myocardial tissue via the administration of a Product to a human patient.

Section 1.37 "Product" shall mean a liquid polymer composed of Sodium Alginate and Ca-D-Gluconate (designated by BioLineRx as "BL-1040"), or any back-ups or second-generation polymers or polymer combinations thereof that is Developed under the Development Program.

Section 1.38 "Regulatory Approval" shall mean, with respect to a jurisdiction, the approval of the applicable Regulatory Authority required to market and sell a Product in such jurisdiction. For clarity, Regulatory Approval for a Product shall occur:

(a) in the United States, on the date when the FDA approves a Premarket Approval (PMA) application;

(b) in Europe, on the date when such Product may first be placed on the market as a medical device (as such terms are defined in Art. 1 Paragraphs 2(a) and (h) of Directive 93/42/EEC, as amended) bearing the CE marking according to Art. 17 of Directive 93/42/EEC, as amended, in any member state of the EU; and

(c) in Japan, on the date when the Ministry of Health approves a marketing authorization.

Section 1.39 "Regulatory Authority" shall mean any national (*e.g.*, the FDA), supra-national or other regulatory agency or governmental entity involved in the granting of Regulatory Approval for, or in the regulation of human clinical studies of, therapeutic medical devices.

Section 1.40 "Royalty Term" shall mean, with respect to a Product in a country of the Territory, the period of time commencing on the First Commercial Sale of such Product in such country and ending upon the earlier of (a) the expiration of the last-to-expire Valid Claim in the BioLineRx Patent Rights that Covers the sale or use of such Product in the Field in such country, or (b) the date of a judicial determination from which no appeal can be taken of invalidity of a set of claims in the BioLineRx Patent Rights that Cover the sale or use of such Product in the Field in such country and that are asserted through litigation (whether in an infringement action, a declaratory judgment action, or otherwise) to exclude a Third Party from selling or using a product in the Field in such country.

Section 1.41 "Sublicensed IP" shall mean that portion of the BioLineRx Intellectual Property licensed to BioLineRx pursuant to the BGN License Agreement.

Section 1.42 "Successful Completion" shall mean:

(a) with respect to the On-Going Phase I/II Trial, no treatment-related safety findings during the treatment period and the six (6) month follow up period, that were considered by the Independent Safety Monitoring Board for the On-Going Phase I/II Trial (in accordance with and subject to the Independent Safety Monitoring Board Charter attached hereto as Schedule 1.42(a)) to be of sufficient concern to discontinue the On-Going Phase I/II Trial;

(b) with respect to the Interim Analysis of the Pivotal Clinical Trial/Phase IIb Proof of Concept, safety and efficacy data from completion of all patients at the [**] follow up demonstrates more than a [**] probability of meeting pre-specified endpoints at [**] in the Pivotal Clinical Trial, and no apparent safety signal in the treatment group for the entire cohort at all times;

(c) with respect to the Pivotal Clinical Trial for the Primary Indication, safety and efficacy data from completion of all patients at the [**] follow up meets the primary endpoint and demonstrates a positive benefit-to-risk ratio to enable FDA submission; and

(d) with respect to all other clinical trials of a Product, that the JDC has determined that the final results of such clinical trial have achieved the success criteria established by the JDC with respect to such clinical trial.

Section 1.43 "Territory" shall mean the entire world.

Section 1.44 "Third Party" shall mean any Person other than a Party or any of its Affiliates or Licensees.

Section 1.45 "Valid Claim" shall mean a claim of any issued, unexpired patent that has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken, or with respect to which an appeal is not taken within the time allowed for appeal, and that has not been disclaimed or admitted to be invalid or unenforceable through reissue, reexamination, disclaimer, or otherwise.

Section 1.46 Additional Definitions. Each of the following terms is defined in the section of this Agreement indicated below:

Term	Section
"Agreement"	Preamble
"Bankruptcy Code"	Section 2.5
"BGN"	Section 1.2
"BioLineRx"	Preamble
"BL-1040"	Section 1.37
"Breaching Party"	Section 8.2
"Combination Product"	Section 1.29
"Commercialization Plan"	Section 3.7
"Competitive Infringement"	Section 5.3(a)
"Effective Date"	Section 2.1
"Existing Product Agreements"	Section 2.3
"Ikaria"	Preamble
"Development Plan"	Section 3.1
"Development Program"	Section 3.1
"Force Majeure Event"	Section 10.7
"Indemnified Party"	Section 10.1(c)
"Indemnifying Party"	Section 10.1(c)
"Invalidity Claim"	Section 5.3(d)
"Joint Development Committee" or "JDC"	Section 3.2
"Joint Manufacturing Committee" or "JMC"	Section 3.6(c)
"Lead Party"	Section 5.3(e)
"Losses"	Section 10.1(a)
"New Indication"	Section 2.4
"New Indication Invention"	Section 5.1(a)
"Non-Breaching Party"	Section 8.2
"OCS"	Section 2.1
"SEC"	Section 6.1
"Severed Clause"	Section 10.11
"Technology Exchange"	Section 3.5
"Technology Exchange Plan"	Section 3.5
"Third Party Payment"	Section 4.2(b)

Section 1.47 Interpretation. Whenever the context may require, any pronoun shall include the corresponding masculine, feminine, and neuter forms. The words "include", "includes" and "including" shall be deemed to be followed by the phrase "without limitation". The word "will" shall be construed to have the same meaning and effect as the word "shall". The word "or" shall be construed to have the same meaning and effect as "and/or". This Agreement has been prepared jointly with the assistance of counsel and shall not be strictly construed against either Party. The captions or headings of the sections or other subdivisions hereof are inserted only as a matter of convenience or for reference and shall have no effect on the meaning of the provisions hereof. Unless the context requires otherwise, (a) any definition of or reference to any agreement, instrument, or other document herein shall be construed as referring to such agreement, instrument, or other document as from time to time amended, supplemented, or otherwise modified (subject to any restrictions on such amendments, supplements, or modifications set forth herein or therein), (b) any reference to any laws herein shall be construed as referring to any law, statute, rule, regulation, ordinance, or other pronouncement having the effect of law of any federal, national, multinational, state, provincial, county, city, or other political subdivision, domestic or foreign, as they from time to time may be enacted, repealed, or amended, (c) any reference herein to any Person shall be construed to include the Person's successors and assigns, (d) the words "herein", "hereof", and "hereunder", and words of similar import, shall be construed to refer to this Agreement in its entirety and not to any particular provision hereof, (e) any reference herein to the words "mutually agree" or "mutual written agreement" shall not impose any obligation on either Party to agree to any terms relating thereto or to engage in discussions relating to such terms except as such Party may determine in such Party's sole discretion, and (f) all references herein to Articles, Sections, Exhibits, or Schedules shall be construed to refer to Articles, Sections, Exhibits, and Schedules of this Agreement.

Article II
Grant of Rights

Section 2.1 BioLineRx License Grant to Ikaria; Consent of OCS. Subject to the terms and conditions of this Agreement, including the consent of the Office of the Chief Scientist of the State of Israel ("OCS"), BioLineRx hereby grants to Ikaria the exclusive, royalty-bearing right and license in the Territory under the BioLineRx Intellectual Property (including, for clarity, a sublicense under the Sublicensed IP) to Develop, Manufacture and Commercialize Products for use in the Field. Subject to the consent of BioLineRx, which consent shall not be unreasonably withheld, conditioned or delayed, the foregoing license includes the right to grant sublicenses under the BioLineRx Intellectual Property, provided that, with respect to sublicenses granted under the Sublicensed IP, Ikaria shall (a) grant such sublicenses only for consideration and at arm's-length transactions, and (b) grant such sublicenses only pursuant to written agreements that contain such terms and conditions as may be required for Ikaria to comply with this Agreement. BioLineRx shall use its best efforts to obtain the written consent of the OCS to this Agreement within [**] days after August 26th, 2009, which consent must be in a form that is satisfactory to each Party. If the OCS has still not provided such consent during such [**] days, Ikaria shall have the right to require BioLineRx to continue to use best efforts to obtain such consent within the subsequent [**] day period. In addition, (i) Ikaria shall have the right to have a representative present at all interactions between BioLineRx's representatives and the OCS relating to such consent, (ii) BioLineRx shall (A) provide Ikaria with a reasonable opportunity to review and approve the request for consent submitted to the OCS and (B) keep Ikaria fully

informed as to the progress of such request for consent and shall consult with Ikaria in good faith with respect thereto, (iii) BioLineRx shall not engage in any activities or discussions with any Third Party relating to the subject matter of this Agreement, including pursuing any other transactions relating to the BioLineRx Intellectual Property, without Ikaria's consent, and (iv) Ikaria shall have the right, prior to the Effective Date, to unilaterally modify this Agreement to comply with the specific, formal, written requests of the OCS, provided that such modifications have no detrimental financial impact on BioLineRx under this Agreement. Notwithstanding BioLineRx's obligation to exercise best efforts to obtain the consent from the OCS as described above, BioLineRx shall not be required to (y) agree to any request by the OCS that would require BioLineRx to pay to the OCS an aggregate amount of more than $[**] or (z) obtain a consent based on the characterization of this Agreement as a "transfer of know-how outside of Israel" under Section 19B of the Israeli Law for the Encouragement of Industrial Research & Development, 1984. Notwithstanding anything herein to the contrary, subject to Section 8.6, the provisions of this Agreement other than this Section 2.1, Section 2.2, Article VII, Section 8.6 and Article X shall not be effective until such consent has been obtained and each Party has delivered the certificate set forth in Section 7.8 (the "Effective Date").

Section 2.2 Non-Competition. During the term of this Agreement, BioLineRx shall not, within the Territory, directly or indirectly (including through its Affiliates), conduct research or discovery activities, Develop, Manufacture (except as set forth in Section 3.6), Commercialize, or grant any rights or options or provide assistance to any Third Party to conduct research or discovery activities, Develop, Manufacture (except as set forth in Section 3.6) or Commercialize, (a) the Product or (b) any compound, substance, polymer, or product (whether pharmaceutical or device in nature) the method of action or effect of which is similar to any Product.

Section 2.3 Existing Product Agreements. BioLineRx hereby agrees that, upon the written request of Ikaria, BioLineRx shall assign to Ikaria each of the agreements listed in Schedule 2.3 attached hereto (the "Existing Product Agreements"), and all of its rights, title, and interest therein. BioLineRx shall cooperate with Ikaria, including by executing and recording documents, as may be necessary to effectuate such assignments and the exercise by Ikaria of its rights under the Existing Product Agreements.

Section 2.4 Intentionally Omitted.

Section 2.5 Section 365(n) of the Bankruptcy Code. All rights and licenses granted under or pursuant to any Section of this Agreement, including under this Article II and with respect to any BioLineRx Intellectual Property subject to Technology Exchange under Section 3.5, are rights to "intellectual property" (as defined in Section 101(35A) of Title 11 of the United States Code (such Title, the "Bankruptcy Code")). Each of Ikaria and BioLineRx hereby acknowledges "embodiments" of such intellectual property for purposes of Section 365(n) of the Bankruptcy Code shall include (a) copies of research data, (b) laboratory samples, (c) product samples, (d) formulas, (e) laboratory notes and notebooks, (f) data and results related to clinical studies, (g) regulatory filings and approvals, (h) rights of reference in respect of regulatory filings and approvals, (i) research data and results, and (j) marketing, advertising, and promotional materials, in each case, that relate to such intellectual property. Each Party shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code or analogous legislation in any other jurisdiction. Upon the institution by or against BioLineRx of any assignment for the

benefit of creditors, composition, or any bankruptcy, reorganization, arrangement, insolvency, or similar proceedings under the laws of any jurisdiction, Ikaria shall further be entitled to a complete duplicate of, or complete access to, as appropriate, any such intellectual property (including embodiments thereof), and such intellectual property and embodiments, if not already in its possession, shall be promptly delivered to Ikaria, unless BioLineRx elects to continue, and continues, to perform all of its obligations under this Agreement.

Section 2.6 Retained Rights. Except as otherwise specifically provided for in this Agreement, each Party retains all rights and licenses to exploit its own intellectual property.

Article III
Development; Manufacturing; Commercialization

Section 3.1 General. Ikaria shall be solely responsible for conducting and funding all Development activities pursuant to the Development Plan, and shall have the sole right to Develop, Manufacture, and Commercialize Products in the Field in the Territory. Subject to its obligations under Section 3.8, Ikaria shall prepare a non-binding plan (the "Development Plan") for the Development of Product(s) (the "Development Program"). The Development Plan shall include an estimated budget setting forth Ikaria's anticipated development costs. Ikaria shall provide BioLineRx with a copy of its then-current Development Plan at least [**] per year, but no later than [**] days following the beginning of each year. The initial Development Plan is attached hereto as Schedule 3.1, which shall be non-binding, including any timelines or milestones that may be included therein. In addition, Ikaria shall, within [**] days after the Effective Date, provide BioLineRx with a revised draft protocol for the Interim Analysis of the Pivotal Clinical Trial/Phase IIb Proof of Concept and the Pivotal Clinical Trial, after taking into account any comments BioLineRx may wish to provide based on the initial draft of the protocol attached hereto as Schedule 1.35, that would include modifications designed to maximize the likelihood of obtaining reasonable reimbursement for one or more Products in any one or more of the following countries [**]. Upon the Successful Completion of the Interim Analysis of the Pivotal Clinical Trial/Phase IIb Proof of Concept, or, failing that, upon the Successful Completion of the Pivotal Clinical Trial, Ikaria shall, within [**] days thereafter, submit a formal written request for a reimbursement price for one or more Product(s) to the applicable governmental agency in one or more of the following countries: [**]

Section 3.2 Joint Development Committee.

(a) The Parties shall establish a Joint Development Committee (the "Joint Development Committee" or "JDC"), comprised of [**] representatives of Ikaria and [**] representatives of BioLineRx, to oversee the Development of Products. Each Party shall make its initial designation of its representatives not later than [**] days after the Effective Date. Each Party may change any one or more of its representatives to the Joint Development Committee at any time upon notice to the other Party.

(b) The JDC shall meet at least [**] during the Development Term or more or less frequently as the JDC may agree. The JDC may meet in person or by means of a telephone or video conference call. One meeting of the JDC per year shall be held in person at Ikaria's

headquarters in Clinton, NJ and one meeting of the JDC per year shall be held in person at BioLineRx's headquarters in Israel, provided, that the Parties' representatives may participate in person, via telephone, or video conference in their discretion. Each Party shall use reasonable efforts to cause its representatives to attend the meetings of the JDC. If a representative of a Party is unable to attend a meeting, such Party may designate an alternate to attend such meeting in place of the absent representative. Each Party shall bear its own costs with respect to its participation on the JDC. Prior to every meeting of the JDC, Ikaria will provide to the JDC detailed reports describing Ikaria's current clinical and development activities and plans.

(c) The JDC shall be the vehicle by which BioLineRx may offer insight and guidance to Ikaria with respect to (i) establishing the Development Plan setting forth the Development Program's objectives and the activities to be conducted, (ii) reviewing and updating the Development Plan from time to time, (iii) monitoring the progress and results of the Development Program, (iv) determining future Development Program activities, including Development activities relating to Manufacturing, to be conducted during the Development Term, and (v) establishing success criteria for the clinical trials (other than those for which success criteria are set forth in this Agreement), and determining whether the results of such clinical trials have achieved the applicable success criteria.

(d) The JDC shall only act unanimously, with each Party given one (1) vote regardless of the number of representatives. If, however, the JDC is unable to reach agreement with respect to any matter within [**] days, the matter shall be referred to the Parties' respective Executive Officers for resolution. If the Executive Officers are not able to resolve any such matter by consensus within [**] days following referral, Ikaria's Executive Officer shall have the right to decide the matter taking into account Ikaria's obligation to use Commercially Reasonable Efforts under Section 3.8.

Notwithstanding anything in this Section 3.2, neither Party shall have a unilateral right to resolve any dispute involving the breach or alleged breach of this Agreement, to amend or modify this Agreement or the Parties' respective rights and obligations hereunder or, except as expressly provided in this Section 3.2, any Development Plan or the Parties' respective rights and obligations thereunder.

Section 3.3 On-Going Trials. BioLineRx shall retain control of, bear all costs relating to the On-Going Phase I/II Trial and the Other On-Going Trials, and shall exercise Commercially Reasonable Efforts to continue and complete the On-Going Phase I/II Trial and the Other On-Going Trials, which shall be managed by BioLineRx. BioLineRx may modify the On-Going Phase I/II Trial and the Other On-Going Trials, including any changes to the protocols therefor, only with the prior written consent of Ikaria, which consent shall not be unreasonably withheld, conditioned or delayed.

Section 3.4 Regulatory Matters. Ikaria shall prepare and submit all filings with Regulatory Authorities relating to Products, which filings shall be in Ikaria's name, provided that Ikaria shall provide BioLineRx [**] days prior notice to enable BioLineRx to review and provide any comments on such submissions. With respect to regulatory matters concerning Products, BioLineRx shall cooperate with Ikaria in the preparation and support of each application for Regulatory Approval and shall provide Ikaria with such reasonable assistance as Ikaria may

request. For example, upon Ikaria's request, BioLineRx shall describe the materials in sufficient and reasonable detail as requested by Ikaria, the Manufacturing techniques and other appropriate characteristics of Products (and the components thereof), and provide Ikaria with such other information related to the Products, including materials, chemistry, Manufacturing, technical dossier and controls data, batch records, analytical and quality control, device master files (if applicable), data from the On-Going Phase I/II Trial or Other On-Going Trials, or other information as Ikaria may reasonably request.

Section 3.5 Technology Exchange.

(a) As soon as reasonably practicable after Ikaria's written request, BioLineRx shall complete the activities assigned to BioLineRx as set forth on the technology exchange plan attached hereto as Exhibit A (the "Technology Exchange Plan"), to effect the transfer to Ikaria (or Ikaria's designee(s)) of all embodiments of and information relating to BioLineRx Intellectual Property reasonably necessary for the exercise of Ikaria's rights under the license granted pursuant to Section 2.1, including the Manufacturing of Products ("Technology Exchange"). BioLineRx shall make available to Ikaria (or Ikaria's designee(s)) such number of technical personnel as may be set forth in the Technology Exchange Plan to answer any questions or provide instruction as reasonably requested by Ikaria (or Ikaria's designee(s)) concerning the items delivered pursuant to this Section 3.5, in connection with the Development, Manufacture and Commercialization of Products hereunder. Each Party shall bear its own costs with respect to the Technology Exchange.

(b) The Joint Development Committee shall be responsible for coordinating the technology exchange activities under the Technology Transfer Plan. Each Party shall cooperate with the other Party in such other Party's conduct of technology exchange activities under the Technology Exchange Plan.

(c) If Ikaria desires that BioLineRx provide technology exchange services beyond the scope of the Technology Exchange Plan, BioLineRx shall provide such services on terms to be agreed upon in good faith by the Parties. Notwithstanding the foregoing, BioLineRx shall provide Ikaria with reasonable access to BioLineRx's employees and consultants involved prior to the Effective Date and during the term of this Agreement with the Development of any Product.

Section 3.6 Manufacturing.

(a) Ikaria shall be solely responsible for the Manufacture of Products for Development or for Commercialization in the Field in the Territory, which Ikaria may conduct itself or through Affiliates or Licensees.

(b) BioLineRx Ltd. shall have the option (either directly or through an Affiliate), exercisable in its sole discretion no later than six (6) months prior to the date on which Ikaria intends to file for Regulatory Approval in the U.S., to Manufacture Product pursuant to the terms of a supply agreement to be negotiated in good faith by the Parties, provided that (i) BioLineRx may exercise the foregoing option only to the extent that it has the demonstrated ability to manufacture the Product, including compliance with cGMP and all applicable laws and

regulations, including those of the FDA and EMEA, (ii) BioLineRx shall bear all expenses required to establish and qualify the BioLineRx manufacturing site, including the costs of scale-up batches, process validation batches and stability batches, (iii) BioLineRx shall not be entitled to assign such option or to utilize subcontract manufacturing, and (iv) neither Party shall have any obligation to enter into such agreement unless all of the terms and conditions thereof are acceptable to both Parties. If BioLineRx Ltd. exercises such option and the Parties enter into a supply agreement, (x) Ikaria shall be required to purchase no less than twenty percent (20%) of its requirements for the Product from BioLineRx, and (y) the per unit price for the Product shall be the [**], provided that the price shall not exceed [**] percent ([**]%) of the Net Sales price per unit of Product; provided, further, that if BioLineRx at any time shall fail to supply Product on time or such supply is otherwise disrupted, the minimum purchase requirement set forth in the preceding clause (x) shall no longer apply. Any clinical supply provided to Ikaria by BioLineRx would be provided at cost.

(c) The Parties will discuss the most efficient structure for the Manufacture and supply of Product for Development and Commercialization purposes. If the Parties determine that coordination in Manufacturing is appropriate, the Parties will establish a Joint Manufacturing Committee (the "Joint Manufacturing Committee" or "JMC") to coordinate Manufacturing efforts. If established, the JMC would be comprised of [**] representatives of Ikaria and [**] representatives of BioLineRx, to oversee the Manufacturing of Products. Each Party would make its initial designation of its representatives not later than [**] days after the Parties agreed to establish the JMC. Each Party shall designate as its representatives individuals who have the requisite experience and knowledge to discuss the Manufacturing of Products. Each Party would be permitted to change any one or more of its representatives to the JMC at any time upon notice to the other Party.

(d) The JMC would meet at least [**] or more or less frequently as the JMC may agree. The location of such meetings shall be as mutually agreed by the Parties. The JMC may also meet by means of a telephone or video conference call. Each Party shall use reasonable efforts to cause its representatives to attend the meetings of the JMC. If a representative of a Party is unable to attend a meeting, such Party may designate an alternate to attend such meeting in place of the absent representative. Each Party would bear its own costs with respect to its participation on the JMC.

(e) The JMC would only act unanimously. If, however, the JMC is unable to reach agreement with respect to any matter within [**] days, the matter shall be referred to the Parties' respective Executive Officers for resolution. If the Executive Officers are not able to resolve any such matter by consensus within [**] days following referral, Ikaria's Executive Officer shall have the right to decide the matter taking into account Ikaria's obligation to use Commercially Reasonable Efforts under Section 3.8.

Section 3.7 Commercialization. Ikaria shall be solely responsible for conducting, itself or through Affiliates or Licensees, the Commercialization of Products in the Field in the Territory, including (a) contracting with customers and booking sales, (b) setting the price and terms and conditions under which a Product may be sold to customers, and (c) handling of managed care accounts, and, subject to Section 1.29, Section 4.2(b), Section 5.2(d), Section 5.3(e) and Section 10.1(b), as between the Parties, Ikaria shall bear all costs associated therewith. Ikaria shall

produce and update from time to time a comprehensive Commercialization plan (the "Commercialization Plan"), which shall include plans for Commercializing Product in each major market in which Ikaria does not then have a presence. The Commercialization Plan shall include a preliminary timeline for the initial Commercialization of Products, which is intended as a planning and informational tool and shall not constitute a binding obligation on Ikaria, and shall be subject to adjustment by Ikaria from time to time, provided, that, Ikaria shall provide BioLineRx with prior written notice of any material proposed change to a timeline. The most recent preliminary Commercialization Plan is attached hereto as Schedule 3.7.

Section 3.8 Efforts. Ikaria shall use Commercially Reasonable Efforts, either itself or through Affiliates or Licensees, (a) to Develop at least one Product in the Territory and (b) to Commercialize at least one Product in the Territory.

Article IV
Financial Provisions

Section 4.1 Milestone Payments.

(a) Development and Regulatory Milestones. With respect to each of the following milestones, Ikaria shall pay BioLineRx the corresponding payment set forth below within [**] days after the achievement by Ikaria, its Affiliates or Licensees of such milestone:

MILESTONE			PAYMENT
1.	Effective Date		$ 7,000,000
2.	Successful Completion of On-Going Phase I/II Trial		$ 10,000,000
3.	[**]		$ [**]
	[**]	$ 12,500,000	
	[**]	$ [**]	
4.	[**]		$ [**]
5.	[**]		$ [**]
6.	[**]		$ [**]
Total Development and Regulatory Milestone Payments			132,500,000

(b) Commercialization Milestones. Ikaria shall pay each of the following milestone payments to BioLineRx within [**] days after the achievement of such milestone:

MILESTONE	PAYMENT
1. Annual Net Sales in Territory exceed $[**] in a Calendar Year	$ [**]
2. Annual Net Sales in Territory exceed $[**] in a Calendar Year	$ [**]
3. Annual Net Sales in Territory exceed $[**] in a Calendar Year	$ [**]

Each of the milestones set forth in Section 4.1(a) and Section 4.1(b) shall be paid only once regardless of the number of Products that achieve such milestone.

Section 4.2 Royalties on Net Sales of Products. During the Royalty Term applicable to each Product, and subject to adjustment as set forth in Section 4.2(b), Ikaria shall pay to BioLineRx royalties on a Product-by-Product basis, with the amount of such royalties calculated as a percentage of Net Sales in a calendar year for such Product as set forth below:

Net Sales	Royalty
Up to $250 Million	11%
>$250 Million to $1 Billion	13%
>$1 Billion	15%

(a) Royalties Payable Only Once. The obligation to pay royalties is imposed only once with respect to Net Sales of the same unit of a Product.

(b) Royalty Reductions for Third Party Payments. Ikaria shall use Commercially Reasonable Efforts to avoid any Third Party Payments. Ikaria shall provide BioLineRx written notice within [**] days of its receipt of any request or demand that Ikaria, its Affiliates or any Licensee obtain a license or immunity from suit from any Third Party in order for Ikaria, its Affiliates, or any Licensee to exercise or use the rights granted to Ikaria herein. If Ikaria is required to obtain a license or immunity from suit from any Third Party in order for Ikaria, its Affiliates, or any Licensee to exercise or use the rights granted to Ikaria herein, and Ikaria, its Affiliates, or any Licensee pays any Third Party any up-front fee, milestone, royalty, or other payment (each, a "Third Party Payment") in connection with such license or immunity from suit, Ikaria shall have the right to set off against any amounts payable to BioLineRx under this Article IV [**] percent ([**]%) of any Third Party Payments provided that in no event will the royalty paid to BioLineRx on Net Sales in the applicable country fall below [**] percent ([**]%). If the amount of Third Party Payments that Ikaria is entitled to set off exceeds the amount otherwise payable to BioLineRx at any given time, or is limited by the foregoing [**] percent ([**]%), Ikaria shall be entitled to carry over the excess for set off against amounts payable to BioLineRx in subsequent periods until Ikaria has been credited for the full amount it is entitled to set off. Prior to paying any Third Party Payment, the Parties shall obtain an analysis from their

respective counsel in respect of the validity of the claim of any Third Party seeking Third Party Payments. If the Parties are unable to agree on an assessment of the claim, the Parties shall jointly engage mutually acceptable independent patent counsel not regularly employed by either Party to assess such claims. Ikaria shall substitute the decision of such independent patent counsel for that of its own counsel with respect to deciding whether to obtain a license or immunity from suit from any Third Party in order for Ikaria, its Affiliates, or any Licensee to exercise or use the rights granted to Ikaria herein.

(c) Duration of Payments. The amounts payable to BioLineRx under Section 4.2 shall be paid on a Product-by-Product and country-by-country basis until the expiration of the Royalty Term for such Product in such country.

(d) Price Concessions. Ikaria shall not, and shall ensure that its Affiliates and Licensees do not, sell or distribute the Product at a discount (including in the form of government mandated rebates) (with or without consideration) in return substantially for (i) concessions or consideration received in transactions involving products or services other than the Product or (ii) concessions from any government or governmental authority relating to products or services other than the Product.

Section 4.3 Reports and Accounting.

(a) Reports; Payments. Ikaria shall deliver to BioLineRx, within [**] days after the end of each calendar quarter, reasonably detailed written accountings of Net Sales of Products that are subject to payment obligations to BioLineRx for such calendar quarter. Such quarterly reports shall indicate (i) gross sales and Net Sales on a country-by-country basis, (ii) the calculation of payment amounts owed to BioLineRx from such gross sales and Net Sales, and (iii) any amounts set off pursuant to Section 4.2(b) against payments owed to BioLineRx. When Ikaria delivers such accounting to BioLineRx, Ikaria shall also deliver all amounts due under Section 4.2 to BioLineRx for the calendar quarter. All payments shall be made by wire transfer to the account specified in Schedule 4.3(a).

(b) Audits by BioLineRx. Ikaria shall keep, and shall require its Affiliates and Licensees to keep, complete and accurate records of the most recent [**] years relating to gross sales and Net Sales and all information relevant under Section 4.1 and Section 4.2. For the sole purpose of verifying amounts payable to BioLineRx, BioLineRx shall have the right no more than [**] per calendar year, at BioLineRx's expense, to engage independent accountants to review such records in the location(s) where such records are maintained by Ikaria, its Affiliates, and its Licensees upon reasonable notice and during regular business hours. Prior to any review conducted pursuant to this Section 4.3(b), BioLineRx's accountants shall have entered into a written agreement with Ikaria limiting the use of such records to verification of the accuracy of payments due under this Agreement and prohibiting the disclosure of any information contained in such records to a Third Party and to BioLineRx for a purpose other than as set forth in this Section 4.3(b). The right to audit any royalty report or quarterly report or payment shall extend for [**] years from the end of the calendar year in which such royalty report or quarterly report was delivered or such payment made. Results of such review shall be made available to Ikaria. If the review reflects an underpayment to BioLineRx, such underpayment shall be promptly remitted to BioLineRx. Likewise, if the review reflects an overpayment, Ikaria shall be entitled

to reduce any subsequent payments by the amount of the overpayment. If the underpayment to BioLineRx is equal to or greater than [**] percent ([**]%) of the amount that was otherwise due, BioLineRx shall be entitled to have Ikaria reimburse BioLineRx's reasonable out-of-pocket costs of such review.

Section 4.4 Currency Amounts. All dollar ($) amounts specified in this Agreement are United States Dollar amounts.

Section 4.5 Currency Exchange. With respect to sales of Products invoiced in U.S. Dollars and other amounts received or paid by Ikaria, its Affiliates or Licensees in U.S. Dollars, such amounts and the amounts payable hereunder shall be expressed in U.S. Dollars. With respect to sales of Products invoiced in a currency other than U.S. Dollars and other amounts received or paid by Ikaria, its Affiliates or Licensees in a currency other than U.S. Dollars, such amounts and the amounts payable hereunder shall be expressed in their U.S. Dollar equivalent calculated using the applicable rate of exchange reported by *The Wall Street Journal* (Eastern U.S. edition) on the last Business Day of the calendar quarter to which the report under Section 4.3(a) relates. All payments hereunder shall be made in U.S. Dollars.

Section 4.6 Tax Withholding. The Parties shall use all reasonable and legal efforts to reduce tax withholding on payments made to BioLineRx. The Parties agree to cooperate in good faith to provide one another with such documents and certifications as are reasonably necessary to enable Ikaria to minimize any withholding tax obligations. Ikaria shall promptly provide to BioLineRx documentation of the payment of any withholding taxes that are paid pursuant to this Section 4.6, including copies of receipts or other evidence reasonably required and sufficient to allow BioLineRx to document such tax withholdings adequately for purposes of claiming foreign tax credits and similar benefits.

Section 4.7 Upfront Payments Received Under Sublicenses. If Ikaria receives an upfront payment consideration under a sublicense granted to a Third Party under this Agreement, Ikaria shall pay to BioLineRx ten percent (10%) of any such payment within 30 days after actual receipt thereof from the Third Party.

Article V
Intellectual Property Ownership, Protection and Related Matters

Section 5.1 Ownership of Inventions.

(a) Intentionally Omitted.

(b) Intentionally Omitted.

(c) Inventorship. Questions of inventorship shall be resolved in accordance with United States patent laws. In the event of a dispute regarding inventorship, if the Parties are unable to resolve the dispute, the Parties shall jointly engage mutually acceptable independent patent counsel not regularly employed by either Party to resolve such dispute. The decision of such independent patent counsel shall be binding on the Parties with respect to the issue of inventorship.

(d) Further Actions and Assignments. Each Party shall take all further actions and execute all assignments requested by the other Party and reasonably necessary or desirable to vest in the other Party the ownership rights set forth in this Section 5.1.

Section 5.2 Prosecution and Maintenance of Patent Rights.

(a) Intentionally Omitted.

(b) BioLineRx Intellectual Property. Upon the Effective Date, Ikaria shall assume responsibility for the management of the preparation, filing prosecution and maintenance of any and all patent applications, including any interference proceedings related thereto, included in the BioLineRx Intellectual Property (including, for clarity, the Sublicensed IP, BioLineRx Patent Rights and patents and patent applications that claim or disclose BioLineRx Know-How).

(c) BioLineRx Step-in Right. If Ikaria, on a country-by-country basis, declines to file and prosecute, or elects not to take actions necessary to avoid abandonment of, any patent applications or maintain any patent in any country, in each case for which it has responsibility under Section 5.2(a) or Section 5.2(b), it shall give BioLineRx reasonable notice to this effect sufficiently in advance to permit BioLineRx to undertake such filing and prosecution without a loss of rights, and thereafter BioLineRx may, upon written notice to Ikaria, file and prosecute such patent applications and maintain such patents in such country. If BioLineRx files, prosecutes or maintains any such patent application or patent in such country and any resulting Valid Claim of BioLineRx Patent Rights constitutes the only BioLineRx Patent Rights Covering the Product in such country (*i.e.,* there are no other BioLineRx Patent Rights Covering the Product in such country), then [**].

If BioLineRx exercises the foregoing step-in right following the election by Ikaria to abandon all existing BioLineRx Patent Rights in a given country, Ikaria shall, within [**] days following BioLineRx's written request, notify BioLineRx in writing whether Ikaria intends to Commercialize a Product in the Field in such country. If Ikaria notifies BioLineRx that Ikaria has no intent to Commercialize a Product in the Field in such country, BioLineRx may, upon written notice to Ikaria within [**] days of receipt of Ikaria's notice of lack of intent, exercise a right to directly Commercialize a Product in the Field in such country. If BioLineRx provides Ikaria with such notice: [**].

(d) Costs and Expenses. Ikaria shall pay the costs and expenses of preparing, filing, prosecuting, and maintaining the Patent Rights covered by Section 5.2(a) or Section 5.2(b), [**].

(e) Cooperation Between Parties. Each Party agrees to cooperate with the other with respect to the preparation, filing, prosecution and maintenance of Patent Rights pursuant to this Section 5.2, including the execution of all such documents and instruments and the performance of such acts as may be reasonably necessary in order to permit the other Party to continue any preparation, filing, prosecution or maintenance of such Patent Rights, including Patent Rights that such Party has elected not to pursue, as provided for in subsections (a), (b) and (c) above. In addition, the filing, prosecuting and maintaining Party in subsections (a), (b) and (c) above shall promptly forward to the other Party copies of any substantive correspondence and actions prepared for or received from the U.S. Patent and Trademark Office or any foreign patent office that may materially affect the Patent Rights being prosecuted or maintained. The other Party's patent counsel may provide comments to the filing, prosecuting and maintaining Party. If any comments by the other Party's patent counsel are provided in sufficient time for the filing, prosecuting and maintaining Party to reflect such comments in its correspondence or response, and such comments are reasonably directed to maximizing the coverage of the claims of the Patent Rights being prosecuted or maintained, the filing, prosecuting and maintaining Party shall reflect such comments in its correspondence or response, if its patent counsel deems it prudent to do so.

(f) Coordination with BioLineRx pursuant to the Sublicensed IP. With respect to any Sublicensed IP which Ikaria is responsible for filing, prosecuting, and maintaining, Ikaria shall:

(i) consult with BioLineRx regarding the preparation, filing, and prosecution of all patent applications, and the maintenance of all patents, included within such Sublicensed IP, including the content, timing, and jurisdiction of the filing of such patent applications and their prosecution, and other details and overall global strategy pertaining to the procurement and maintenance of Patent Rights in such Sublicensed IP, and shall file, prosecute, and maintain all such Patent Rights through a law or patent attorney firm selected by Ikaria and approved by BioLineRx (and BioLineRx shall exercise its rights under the BGN License Agreement as may be necessary to obtain BGN's approval); and

(ii) provide BioLineRx with copies of all patent applications that claim or disclose such Sublicensed IP, and BioLineRx shall exercise its rights under the BGN License Agreement to ensure that BGN cooperates in a timely manner with Ikaria's efforts to register such Patent Rights, including by causing BGN to execute any documents as may be required for such purpose.

BioLineRx shall take all actions required to remain in compliance with the BGN License Agreement in connection with the foregoing.

Section 5.3 Third Party Infringement.

(a) Notice. Each Party shall promptly report in writing to the other Party during the term of this Agreement any (i) known or suspected infringement of any of the BioLineRx Patent

Rights or (ii) unauthorized use of any of the BioLineRx Know-How of which such Party becomes aware, including, in the case of either clause (i) or clause (ii) involving, or that may reasonably lead to, the Development, Manufacture, use or Commercialization of a product or product candidate that is or may be competitive with a Product in the Field ("Competitive Infringement"), and shall provide the other Party with all available evidence supporting such infringement, suspected infringement, unauthorized use or suspected unauthorized use.

(b) BioLineRx Intellectual Property; Step-in Rights.

(i) Ikaria shall have the first right, but not the obligation, to initiate a suit or take other appropriate action that either Party reasonably believes is required to protect BioLineRx Intellectual Property from Competitive Infringement . Ikaria shall give BioLineRx sufficient advance notice of its intent to file any such suit or take any such action, and the reasons therefor, and shall provide BioLineRx with an opportunity to make suggestions and comments regarding such suit or action. Thereafter, Ikaria shall keep BioLineRx informed, and shall from time to time consult with BioLineRx regarding the status of any such suit or action and shall provide BioLineRx with copies of all material documents (*i.e.*, complaints, answers, counterclaims, material motions, orders of the court, memoranda of law and legal briefs, interrogatory responses, depositions, material pre-trial filings, expert reports, affidavits filed in court, transcripts of hearings and trial testimony, trial exhibits and notices of appeal) filed in, or otherwise relating to, such suit or action. Any recovery obtained as a result of any proceeding pursuant to this subsection (b)(i), by settlement or otherwise, shall be applied in the following order of priority: (A) first, each Party shall be reimbursed, on a pro rata basis, for all costs incurred by such Party in connection with such suit; and (B) second, [**].

(ii) If Ikaria chooses not to initiate a suit or take other appropriate action under subsection (b)(i) above to protect BioLineRx Intellectual Property from Competitive Infringement, Ikaria will so notify BioLineRx of its intention, in which case BioLineRx shall have the right to initiate such suit or take such other appropriate action. BioLineRx shall give Ikaria sufficient advance notice of its intent to file any such suit or take any such action, and the reasons therefor, and shall provide Ikaria with an opportunity to make suggestions and comments regarding such suit or action. Thereafter, BioLineRx shall keep Ikaria informed, and shall from time to time consult with Ikaria regarding the status of any such suit or action and shall provide Ikaria with copies of all material documents (*i.e.*, complaints, answers, counterclaims, material motions, orders of the court, memoranda of law and legal briefs, interrogatory responses, depositions, material pre-trial filings, expert reports, affidavits filed in court, transcripts of hearings and trial testimony, trial exhibits and notices of appeal) filed in, or otherwise relating to, such suit or action. Any recovery obtained as a result of any proceeding pursuant to this subsection (b)(ii), by settlement or otherwise, shall be applied in the following order of priority: (A) first, each Party shall be reimbursed, on a pro rata basis, for all costs incurred by such Party in connection with such suit; and (B) second, any remainder shall be shared [**]% for BioLineRx and [**]% for Ikaria.

(iii) If BioLineRx chooses not to initiate a suit or take other appropriate action under subsection (b)(ii) above to protect Sublicensed IP from Competitive Infringement and

BGN exercises its rights under the BGN License Agreement to prosecute, prevent, or terminate such Competitive Infringement, any amount received by BioLineRx in connection therewith, whether by settlement or otherwise, [**].

(c) Claimed Infringement. If a Party becomes aware of any claim that the Development, Manufacture, or Commercialization of Products for use in the Field in the Territory infringes Patent Rights or any other intellectual property rights of any Third Party, such Party shall promptly notify the other Party. In any such instance, Ikaria shall have the exclusive right to settle such claim.

(d) Patent Invalidity Claim. If a Third Party at any time asserts a claim that any BioLineRx Patent Rights is invalid or otherwise unenforceable (an "Invalidity Claim"), whether (i) as a defense in an infringement action brought by Ikaria or BioLineRx pursuant to subsection (b) above, or (ii) in an action brought against Ikaria or BioLineRx referred to in subsection (c) above, or (iii) otherwise, the Parties shall cooperate with each other in preparing and formulating a response to such Invalidity Claim. Neither Party shall settle or compromise any Invalidity Claim without the consent of the other Party, which consent shall not be unreasonably withheld, conditioned or delayed.

(e) Conduct of Certain Actions; Costs. Ikaria shall have the sole and exclusive right to select counsel for any suit initiated by it referenced in subsection (b)(i) above or against it referenced in subsection (c) above, and BioLineRx shall have the sole and exclusive right to select counsel for any suit initiated by it referenced in subsection (b)(ii) above. If required under applicable law in order for a Party (the "Lead Party") to initiate or maintain such suit, the other Party shall join as a party to the suit. Such other Party shall offer reasonable assistance to the Lead Party in connection therewith at no charge to the Lead Party except for reimbursement of such other Party's reasonable out-of-pocket expenses incurred in rendering such assistance. The Lead Party shall assume and pay all of its own out-of-pocket costs incurred in connection with any litigation or proceedings referenced in the first sentence of this subsection (e), including the fees and expenses of the counsel selected by it. Subject to applicable law, the other Party shall have the right to participate and be represented in any such suit by its own counsel at its own expense.

(f) Coordination with BGN. With respect to any suit to protect Sublicensed IP from infringement for which Ikaria is the Lead Party, notwithstanding anything to the contrary in this Section 5.3:

(i) if required under applicable law in order for Ikaria to initiate or maintain such suit, BioLineRx shall (A) exercise its rights under the BGN License Agreement to cause BGN to join as a party to such suit, (B) exercise its rights under the BGN License Agreement to obtain BGN's approval of counsel selected by Ikaria to represent Ikaria and BGN in such suit, and (C) [**];

(ii) Ikaria shall not compromise or settle such suit without the prior written consent of BGN, which consent BioLineRx shall exercise its rights under the BGN License Agreement to obtain; and

(iii) any recovery obtained by Ikaria as a result of such suit, by settlement or otherwise, shall be applied in the following order of priority: (A) first, each Party shall be reimbursed, on a pro rata basis, for all costs incurred by such Party in connection with such suit (for clarity, BioLineRx shall be reimbursed for any costs of BGN paid by BioLineRx in accordance with clause (i)(C) above); (B) second, [**] percent ([**]%) of any remainder shall paid to BioLineRx for remittance to BGN as provided in Section 10.1.2 of the BGN License Agreement ; and (C) third, the remaining [**] percent ([**]%) shall be retained by Ikaria; [**].

Article VI
Confidentiality; Non-Solicitation; Standstill

Section 6.1 Confidential Information. Each Party agrees that all Confidential Information disclosed to it or its Affiliates by the other Party (a) shall not be used by the receiving Party or its Affiliates except to fulfill its obligations or exercise its rights under this Agreement, (b) shall be maintained in confidence by the receiving Party and its Affiliates, and (c) shall not be disclosed by the receiving Party or its Affiliates to any Third Party who is not a consultant of, or an advisor to, the receiving Party or its Affiliates without the prior written consent of the disclosing Party, which consent the disclosing Party may withhold in its sole discretion. Notwithstanding the foregoing, either Party may disclose Confidential Information of the other Party if such Party is required to make such disclosure by applicable law, regulation or legal process, including by Israeli securities laws, the rules or regulations of the United States Securities and Exchange Commission (the "SEC") or any similar regulatory agency in a country other than the United States or of any stock exchange, including the Tel Aviv Stock Exchange, in which event such Party shall provide prior notice of such intended disclosure to such other Party, if possible under the circumstances, and shall disclose only such Confidential Information of the other Party as is required to be disclosed. If this Agreement shall be included in any report, statement or other document filed by either Party or an Affiliate of either Party pursuant to the preceding sentence, such Party shall use, or shall cause its Affiliate, as the case may be, to use, reasonable efforts to obtain confidential treatment from the SEC, similar regulatory agency or stock exchange of any financial information or other information of a competitive or confidential nature, and shall include in such confidentiality request such provisions of this Agreement as may be reasonably requested by the other Party.

Section 6.2 Disclosures to Employees, Consultants, Advisors, Etc. Each Party agrees that it and its Affiliates shall provide Confidential Information received from the other Party only to the receiving Party's respective employees, consultants, advisors, Licensees and potential Licensees, and to the employees, consultants and advisors of the receiving Party's Affiliates, who have a need to know such Confidential Information to assist the receiving Party in fulfilling its obligations under this Agreement and only under conditions of confidentiality and non-use at least as stringent as the conditions imposed by this Agreement, provided that BioLineRx and Ikaria shall each remain responsible for any failure by its and its Affiliates' respective employees, consultants, advisors, Licensees and potential Licensees to treat such information and materials as required under Section 6.1. For clarity, (a) Ikaria is permitted to disclose Confidential Information to actual or potential Licensees, acquirors or financing sources; and (b) BioLineRx is permitted to disclose this Agreement and the Development Plan to BGN, solely to

the extent required under the BGN License Agreement; provided that any such disclosure subjects the receiving Third Party to conditions of confidentiality and non-use at least as stringent as the conditions imposed by this Agreement.

Section 6.3 Non-Solicitation. During the term of this Agreement and continuing for [**] months after the termination of this Agreement, neither Party shall directly or indirectly, for its own account or for the account of others, urge, induce, entice, or in any manner whatsoever solicit any employee directly involved in the activities conducted pursuant to this Agreement to leave the employment of the other Party or any of its Affiliates. For purposes of the foregoing, "urge", "induce", "entice" or "solicit" shall not be deemed to mean: (a) circumstances where an employee of a Party initiates contact with the other Party or any of its Affiliates with regard to possible employment; or (b) general solicitations of employment not specifically targeted at employees of a Party or any of its Affiliates, including responses to general advertisements.

Section 6.4 Standstill. Neither Ikaria nor any of its Affiliates shall directly or indirectly, for its own account or for the account of others, acquire more than [**] of the equity or debt securities of BioLineRx, or urge, induce, entice or solicit any Third Party to acquire the equity or debt securities of BioLineRx, in either case without the consent of BioLineRx, which may be withheld in its sole discretion. The obligations of Ikaria under this Section 6.4 shall terminate in the event that (a) any Third Party initiates a tender or exchange offer, or otherwise publicly proposes or agrees to acquire, a majority of the equity or debt securities of BioLineRx (provided that the restrictions set forth in this Section 6.4 shall be reinstated in the event that such tender or exchange offer, or proposal, is terminated or withdrawn), (b) it is publicly disclosed that voting securities representing at least [**] of the total voting power of BioLineRx have been acquired by any one or more Third Parties, (c) BioLineRx publicly announces that it intends to seek a Third Party acquirer (provided that the restrictions set forth in this Section 6.4 shall be reinstated in the event that BioLineRx publicly announces that it no longer is seeking a Third Party acquirer and so notifies Ikaria in writing), (d) BioLineRx enters into any agreement to merge with, or sell or dispose of [**] or more of its assets or securities, or (e) this Agreement is terminated pursuant to Article VIII. BioLineRx shall provide Ikaria with prompt written notice of the occurrence of any of the foregoing events to the extent permitted under applicable law. For clarity, the acquisition by any employee benefit plan of Ikaria or its Affiliates in any diversified index, mutual or pension fund, which fund in turn holds BioLineRx securities, shall not be deemed a breach of this Section 6.4.

Section 6.5 Term. All obligations of confidentiality imposed under this Article VI shall survive until the date that is [**] years after the expiration or termination of this Agreement.

Section 6.6 Publicity. During the term of this Agreement, the content of any press release or public announcement relating to this Agreement or a Product shall be mutually approved by the Parties, except that (a) a Party may issue such press release or public announcement if the contents of such press release or public announcement have previously been made public other than through a breach of this Agreement by the issuing Party, (b) a Party may issue such a press release or public announcement if it is advised by counsel that such press release or public announcement is required by applicable law, regulation or legal process, including by Israeli securities laws, the rules or regulations of the SEC or any similar regulatory agency in a country

other than the United States or of any stock exchange, including the Tel Aviv Stock Exchange, and (c) Ikaria shall remain free to issue press releases and public announcements regarding the Development, Manufacturing, Commercialization and use of Products in the Field, provided that Ikaria shall provide BioLineRx with advance notice of at least [**] days prior to public disclosure of such releases and announcements or such shorter period as required to comply with any applicable law. In addition, BioLineRx shall reasonably implement any changes that Ikaria may recommend with respect to any filing to be made in accordance with the rules or regulations of the SEC or any similar regulatory agency in a country other than the United States or of any stock exchange, including the Tel Aviv Stock Exchange; provided that such Ikaria shall only have the right to comment upon portions of such filings that directly related to Ikaria or this Agreement. Nothing in the foregoing shall require BioLineRx to implement any change that Ikaria may recommend that is not consistent with the rules or regulations of the Israel Securities Authority, Tel Aviv Stock Exchange, the rules or regulations of the SEC, or any similar regulatory agency in a country other than the United States or Israel, as advised in writing by BioLineRx's legal counsel. BioLineRx's legal counsel will provide Ikaria confirmation of such advise.

Section 6.7 Publications. The results of the Development Program may be published by a Party as part of a scientific presentation or publication only after scientific review by and approval of the Joint Development Committee unless the other Party, acting reasonably, disapproves of the presentation or publication in writing within [**] days after receipt of the presentation or publication. Either Party may require that such Party's Confidential Information be redacted from such presentation or publication and may reasonably require that other information also be redacted. In addition, at the request of either Party, the date of submission for presentation or publication shall be delayed for a period of time sufficiently long to permit a Party to seek appropriate patent protection. Other than as provided for herein, BioLineRx shall not make any publication regarding any Product or containing any Confidential Information of Ikaria without the prior written consent of Ikaria. Notwithstanding the foregoing, to the extent necessary or appropriate as determined in Ikaria's discretion, Ikaria may disclose information otherwise covered by this Section 6.7 in documents filed with the SEC.

Article VII
Representations and Warranties

Section 7.1 Representations of Authority. BioLineRx and Ikaria each represents and warrants to the other Party that, except for the consent of the OCS, it has full corporate right, power and authority to enter into this Agreement and to perform its respective obligations under this Agreement and that it has the right to grant to the other Party the rights and licenses granted pursuant to this Agreement.

Section 7.2 Consents. BioLineRx and Ikaria each represents and warrants to the other Party that, except for the consent of the OCS, all necessary consents, approvals and authorizations of all government authorities and other Persons required to be obtained by it as of the date hereof in connection with the execution, delivery and performance of this Agreement have been obtained.

Section 7.3 No Conflict. BioLineRx and Ikaria each represents and warrants to the other Party that, notwithstanding anything to the contrary in this Agreement, except for the consent of the OCS, the execution and delivery of this Agreement, the performance of such Party's obligations in the conduct of the collaboration and the licenses and rights to be granted pursuant to this Agreement (a) do not conflict with or violate any requirement of applicable laws or regulations existing as of the date hereof and (b) do not conflict with, violate, breach or constitute a default under any contractual obligations of such Party or any of its Affiliates existing as of the date hereof.

Section 7.4 Enforceability. BioLineRx and Ikaria each represents and warrants to the other Party that this Agreement is a legal and valid obligation binding upon it and is enforceable against it in accordance with its terms.

Section 7.5 Additional BioLineRx Representations. BioLineRx represents and warrants to Ikaria that:

(a) BioLineRx has the right to grant the licenses granted to Ikaria on the terms set forth in this Agreement;

(b) BioLineRx is not engaged with any Third Party in any Development efforts directed to Products in the Field in the Territory other than with respect to the On-Going Phase I/II Trial, the Other On-Going Trials or the Existing Product Agreements;

(c) BioLineRx has provided Ikaria with true and complete copies of each of the Existing Product Agreements, each of which is in full force and effect in accordance with its terms as of the date hereof, and has obtained all consents necessary for the assignment to Ikaria of each of the Existing Product Agreements hereunder, and, following such assignment, Ikaria shall have the legal right to exercise all rights of BioLineRx that existed thereunder immediately prior to such assignment;

(d) to BioLineRx's Knowledge, the BioLineRx Patent Rights listed in Exhibit B are valid and enforceable and constitute all of the Patent Rights necessary or useful for Ikaria to fully exercise and enforce its rights hereunder;

(e) to BioLineRx's Knowledge, the BioLineRx Patent Rights are not being infringed and the BioLineRx Know-How is not being misappropriated by any Third Party;

(f) BioLineRx owns the entire right, title and interest in and to the BioLineRx Intellectual Property (other than the Sublicensed IP) free and clear of any liens, charges, claims and encumbrances, and no other Person has any claim of ownership or right to obtain compensation with respect to such BioLineRx Intellectual Property;

(g) to BioLineRx's Knowledge, the Products developed in the Development Program and the Development, Manufacture and Commercialization of such Products will not infringe or misappropriate any intellectual property rights not licensed to Ikaria hereunder; and

(h) BioLineRx has not received and has no Knowledge of any claim or demand of any Person pertaining to, or any proceeding which is pending or threatened that asserts, the

invalidity, misuse or unenforceability of the BioLineRx Patent Rights or that challenges BioLineRx's ownership of the BioLineRx Intellectual Property or that makes any adverse claim with respect thereto, and, to the Knowledge of BioLineRx, there is no basis for any such claim, demand or proceeding.

Section 7.6 BGN License Agreement. BioLineRx represents, warrants and covenants to Ikaria that:

(a) BioLineRx has provided Ikaria with a true and complete copy of the BGN License Agreement, which is in full force and effect in accordance with its terms as of the date hereof;

(b) BioLineRx shall obtain and provide to Ikaria within ten (10) days of execution of this Agreement a written statement from BGN certifying that the terms of this Agreement are consistent with those of the BGN License Agreement, including in the context of Section 13.4.1(c) thereof;

(c) BioLineRx has (i) achieved by its designated performance date each Milestone (as that term is defined in the BGN License Agreement) having a designated performance date on or before the date hereof, or obtained a waiver in respect thereof, and (ii) neither (A) committed any material breach of the its obligations under the BGN License Agreement nor (B) received any notice from BGN of any alleged material breach thereof by BioLineRx or of any Failure (as that term is defined therein);

(d) BioLineRx shall upon receipt by BioLineRx promptly provide Ikaria with a copy of any notice from BGN described in the foregoing clause (c)(ii)(B);

(e) BioLineRx shall not terminate, amend, supplement or otherwise modify the BGN License Agreement without Ikaria's prior written consent;

(f) the rights and obligations of BioLine Jerusalem L.P. under the BGN License Agreement have been assigned and delegated, or otherwise transferred, to BioLineRx;

(g) as between BioLineRx and Ikaria, BioLineRx shall be responsible for any and all payments to be made under the BGN License Agreement;

(h) in the event of any termination of the BGN License Agreement, BioLineRx shall, at Ikaria's request, provide all reasonable assistance to Ikaria in Ikaria's efforts to obtain from BGN an exclusive license to the Sublicensed IP, including through enforcement of the provisions of Sections 5.2.3 and 13.4.1(c) of the BGN License Agreement.

Section 7.7 Employee, Consultant and Advisor Legal Obligations. BioLineRx and Ikaria each represents and warrants that each of its and its Affiliates' employees, consultants and advisors who is or will be involved in performing any obligations hereunder has executed or will have executed an agreement or have an existing obligation under law requiring assignment to such Party of all intellectual property made during the course of and as the result of his, her or its association with such Party or such Affiliate, and obligating such employee, consultant or advisor to maintain the confidentiality of Confidential Information to the extent required under

Article VI. BioLineRx and Ikaria each represents and warrants that, to its Knowledge, none of its or its Affiliates' employees, consultants or advisors who is or will be involved in performing any obligations hereunder is, as a result of the nature of such obligations to be performed by the Parties, in violation of any covenant in any contract relating to non-disclosure of proprietary information, non-competition or non-solicitation.

Section 7.8 Accuracy of Representations and Warranties on Effective Date. The representations and warranties of each of the Parties set forth in the preceding sections of this Article VII remain true and accurate on and as of the Effective Date. Each Party shall promptly following receipt of acceptable consent from the OCS deliver to the other Party a certificate to such effect executed by its Chief Executive Officer.

Section 7.9 No Warranties. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, THE PARTIES MAKE NO REPRESENTATIONS AND EXTEND NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING THAT ANY PRODUCTS WILL BE ECONOMICALLY OR TECHNICALLY UTILIZABLE, THAT ANY SALES OF ANY PRODUCTS WILL OCCUR, THAT THE DEVELOPMENT PROGRAM ACTIVITIES WILL BE COMPLETED IN THE EXPECTED TIMEFRAME, OR THAT ANY PRODUCT WILL BE FREE OF ANY THIRD PARTY RIGHTS.

Article VIII
Term and Termination

Section 8.1 Term. The term of this Agreement shall begin on the Effective Date, may be terminated as set forth in this Article VIII, and shall expire on a Product-by-Product and country-by-country basis upon the date of expiration of the Royalty Term for such Product in such country, and shall expire in its entirety upon the last-to-expire Royalty Term, unless earlier terminated as set forth in this Article VIII.

Section 8.2 Termination for Material Breach. Upon any breach of a material provision of this Agreement by a Party (the "Breaching Party"), the other Party (the "Non-Breaching Party") may terminate this Agreement by providing ninety (90) days written notice to the Breaching Party specifying the material breach. The termination shall become effective at the end of the notice period unless the Breaching Party cures such breach during such notice period. Ikaria may terminate this Agreement pursuant to this Section 8.2 immediately upon any termination of the BGN License Agreement.

Section 8.3 Development-Related Termination. Ikaria shall have the right to terminate this Agreement upon sixty (60) days prior written notice, if Ikaria at any time determines, in its sole judgment, that the results of the Development Program do not warrant further Development of Products.

Section 8.4 Effect of Certain Terminations and Expiration.

(a) If this Agreement is terminated by Ikaria under Section 8.2:

(i) The licenses granted by BioLineRx to Ikaria under Section 2.1 and, notwithstanding any other provision in this Agreement to the contrary, Ikaria's obligations under Section 4.2, shall survive;

(ii) Section 2.2 shall survive until Ikaria is no longer obligated to pay royalties to BioLineRx under Section 4.2; and

(iii) Section 5.1 and Section 5.3 shall survive.

(b) If this Agreement is terminated by either BioLineRx under Section 8.2, or by Ikaria under Section 8.3, the licenses granted under Section 2.1 shall terminate as of the effective date of such termination; provided, however, that Ikaria, its Affiliates, and its Licensees shall be afforded a commercially reasonable period of time (but no less than [**] months) to sell off any then existing or in process stocks of the Products, subject to the terms and conditions of this Agreement, including the payment of royalties thereon.

(c) Upon any termination or expiration of this Agreement, each Party shall return to the other Party any tangible property owned by the other Party, including any books and records and Confidential Information, in accordance with the reasonable instructions given by the other Party, with any shipping costs to be borne by the other Party, provided, however, that a Party may retain a copy of any regulatory records it is required to maintain in accordance with applicable law.

Section 8.5 Survival. In the event of any expiration or termination of this Agreement, (a) all financial obligations under Article IV and Article V owed as of the effective date of such expiration or termination shall remain in effect, including such obligations that have accrued, but have not been invoiced, as of such effective date, and (b) the obligations set forth in Section 5.1, Article VI, Article IX and Article X, and all other terms, provisions, representations, rights and obligations contained in this Agreement that by their express terms survive expiration or termination of this Agreement (including Section 8.4 and this Section 8.5), shall survive and all other terms, provisions, representations, rights and obligations contained in this Agreement shall terminate.

Section 8.6 Termination Prior to Effective Date. Notwithstanding anything to the contrary in this Article VIII, Ikaria may terminate this Agreement prior to the Effective Date, with no liability to BioLineRx, if the OCS does not consent to the Agreement in a form reasonably satisfactory to both Parties within forty-five (45) days after the execution of this Agreement. The provisions of Article X (except for Section 10.1(a)) and this Section 8.6 shall survive such termination, and all other terms, provisions, representations, rights and obligations contained in this Agreement shall terminate.

Article IX
Dispute Resolution

Section 9.1 Negotiation. Any controversy, claim or dispute arising out of or relating to this Agreement shall be settled, if possible, through good faith negotiations between the Parties.

Section 9.2 Escalation. If the Parties are unable to settle any dispute after good faith negotiations pursuant to Section 9.1 after [**] days, such dispute (except for any matter that by its express terms shall be resolved as provided in this Agreement, including any matter arising under Section 3.2 or Section 3.6) shall be referred to the Executive Officers to be resolved by negotiation in good faith as soon as is practicable but in no event later than [**] days after referral.

Section 9.3 Mediation. Solely with respect to a dispute as to whether Ikaria has breached its obligations to use Commercially Reasonable Efforts as set forth in Section 3.8, if the Executive Officers are unable to settle such dispute after good faith negotiations pursuant to Section 9.2 within [**] days after referral to the Executive Officers, the Parties shall, within [**] days thereof, engage a mutually agreeable Third Party mediator on a non-binding basis to assist the Parties in determining whether such a breach has occurred. The Parties agree that they will participate in good faith in an effort to resolve the dispute in an informal, inexpensive and expeditious manner and that any mediator selected shall agree to render any judgments in a timely manner, but no later than [**] days after the mediator is selected. All expenses of the mediator will be shared equally by the Parties.

Section 9.4 Litigation. If the Executive Officers are unable to settle any dispute after good faith negotiations pursuant to Section 9.2 (other than a dispute as to whether Ikaria has breached its obligations to use Commercially Reasonable Efforts as set forth in Section 3.8) within [**] days after referral, or if the Parties continue to dispute whether Ikaria has breached its obligations to use Commercially Reasonable Efforts as set forth in Section 3.8 following mediation pursuant to Section 9.3, then either Party may seek resolution of the dispute (except for any matter that by its express terms shall be resolved as provided in this Agreement, including any matter arising under Section 3.2 or Section 3.6) through remedies available at law or in equity from any court of competent jurisdiction as set forth in Section 10.3.

Section 9.5 Equitable Relief. Each Party acknowledges and agrees that the other Party would be damaged irreparably if any of the provisions of Article II, Article V and Article VI are not performed in accordance with their specific terms or otherwise are breached. Accordingly, each Party agrees that the other Party shall be entitled to an injunction or other equitable relief to prevent breaches of such provisions, to preserve status quo, and to enforce specifically such provisions in any action instituted in any court having jurisdiction over the Parties and the matter, in addition to any other remedy to which it may be entitled, at law or in equity.

Article X
Miscellaneous Provisions

Section 10.1 Indemnification.

(a) By Ikaria. Ikaria agrees to defend BioLineRx, its Affiliates and their respective directors, officers, employees and agents at Ikaria's cost and expense, and shall indemnify and hold harmless BioLineRx and its Affiliates and their respective directors, officers, employees and agents from and against any liabilities, losses, costs, damages, fees or expenses (collectively, "Losses") arising out of any Third Party claim to the extent relating to (i) any breach by Ikaria of any of its representations, warranties or obligations pursuant to this Agreement, or (ii) personal

injury, property damage, product liability or other damage resulting from the Development, Manufacture, use or Commercialization of a Product by Ikaria or its Affiliates or Licensees, excluding any claim for which BioLineRx indemnifies Ikaria under subsection (b) below.

(b) By BioLineRx. BioLineRx agrees to defend Ikaria, its Affiliates and their respective directors, officers, employees and agents at BioLineRx's cost and expense, and shall indemnify and hold harmless Ikaria and its Affiliates and their respective directors, officers, employees and agents from and against any Losses arising out of any Third Party claim to the extent relating to (i) any breach by BioLineRx of any of its representations, warranties or obligations pursuant to this Agreement, (ii) personal injury, property damage or other damage resulting from the conduct of the On-Going Phase I/II Trial or the Other On-Going Trials by or on behalf of BioLineRx or its Affiliates, (iii) the BGN Agreement, or (iv) any allegation that the practice of the BioLineRx Intellectual Property rights in the Development Program infringes or misappropriates any Third Party intellectual property rights, to the extent BioLineRx had Knowledge that such practice would infringe or misappropriate such Third Party intellectual property rights on or before the Effective Date.

(c) Claims for Indemnification. A Person entitled to indemnification under this Section 10.1 (an "Indemnified Party") shall give prompt written notification to the Party from whom indemnification is sought (the "Indemnifying Party") of the commencement of any action, suit or proceeding relating to a Third Party claim for which indemnification may be sought or, if earlier, upon the assertion of any such claim by a Third Party (it being understood and agreed, however, that the failure by an Indemnified Party to give notice of a Third Party claim as provided in this Section 10.1(c) shall not relieve the Indemnifying Party of its indemnification obligation under this Agreement except and only to the extent that such Indemnifying Party is actually damaged as a result of such failure to give notice). Within [**] days after delivery of such notification, the Indemnifying Party may, upon written notice thereof to the Indemnified Party, assume control of the defense of such action, suit, proceeding or claim with counsel reasonably satisfactory to the Indemnified Party. If the Indemnifying Party does not assume control of such defense, the Indemnified Party shall control such defense. The Party not controlling such defense may participate therein at its own expense. The Party controlling such defense shall keep the other Party advised of the status of such action, suit, proceeding or claim and the defense thereof and shall consider recommendations made by the other Party with respect thereto. The Indemnified Party shall not agree to any settlement of such action, suit, proceeding or claim without the prior written consent of the Indemnifying Party, which consent the Indemnifying Party shall not unreasonably withhold, condition or delay. The Indemnifying Party shall not agree, without the prior written consent of the Indemnified Party, which consent the Indemnified Party shall not unreasonably withhold, condition or delay, to any settlement of such action, suit, proceeding or claim or consent to any judgment in respect thereof that does not include a complete and unconditional release of the Indemnified Party from all liability with respect thereto or that imposes any liability or obligation on the Indemnified Party.

Section 10.2 Governing Law. This Agreement shall be construed and the respective rights of the Parties determined in accordance with the laws of the State of New York, USA (other than any principle of conflict or choice of laws that would cause the application of the laws of any other jurisdiction).

Section 10.3 Submission to Jurisdiction. Each Party (a) submits to the jurisdiction of any state or federal court sitting in the State of New York, USA in any action or proceeding arising out of or relating to this Agreement, (b) agrees that all claims in respect of such action or proceeding may be heard and determined in any such court, (c) waives any claim of inconvenient forum or other challenge to venue in such court, and (d) agrees not to bring any action or proceeding arising out of or relating to this Agreement in any other court, unless the state or federal courts sitting in the State of New York decline to exercise jurisdiction over any such action or proceeding or if those courts lack proper jurisdiction, then any action or proceeding arising out of or relating to this Agreement may be brought in any other U.S. court of competent jurisdiction. Each Party agrees to accept service of any summons, complaint or other initial pleading made in the manner provided for the giving of notices in Section 10.6, provided that nothing in this Section 10.3 shall affect the right of either Party to serve such summons, complaint or other initial pleading in any other manner permitted by law.

Section 10.4 Assignment. Ikaria may assign this Agreement or any right hereunder, or delegate any obligation hereunder, in its sole discretion, to (a) any Affiliate of Ikaria or (b) any entity acquiring all or substantially all of the assets of Ikaria Holdings, Inc. and its Affiliates. All other assignments by Ikaria, including (i) to any entity acquiring all or substantially all of the assets of Ikaria to which this Agreement relates or (ii) to any entity with which or into which Ikaria may consolidate or merge, are subject to BioLineRx's prior approval, which approval shall not be unreasonably withheld, conditioned or delayed. BioLineRx may assign its right to receive payments hereunder to a Third Party, in its sole discretion, but BioLineRx shall not otherwise be permitted to assign this Agreement, in whole or in part, without the prior written consent of Ikaria, which approval shall not be unreasonably withheld, conditioned or delayed. Any assignments in contravention of this Section 10.4 shall be null and void.

Section 10.5 Entire Agreement; Amendments. This Agreement constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes all previous arrangements between the Parties with respect to the subject matter hereof, whether written or oral, except for that certain Mutual Non Disclosure Agreement between the Parties dated February 25, 2009. Without limiting the generality of the foregoing, this Agreement hereby supersedes and replaces in its entirety the License and Commercialization Agreement by and among the parties dated as of July 5th, 2009. To the extent that any provision of this Agreement conflicts with any provisions of such Mutual Non Disclosure Agreement, the provision of this Agreement shall control. Except as set forth in Section 2.1(iv), any amendment or modification to this Agreement shall be made in writing signed by both Parties.

Section 10.6 Notices.

Notices to Ikaria shall be addressed to:

Ikaria Development Subsidiary One LLC
6 State Route 173
Clinton, NJ 08809, USA
Attention: Chief Executive Officer

with copy to:

Ikaria Holdings, Inc.
6 State Route 173
Clinton, NJ 08809, USA
Attention: General Counsel

Notices to BioLineRx Ltd. shall be addressed to:

BioLineRx Ltd.
19 Hartum Street
P.O. Box 45158
Jerusalem 91450, Israel
Attention: Chief Executive Officer

with copy to:

Arent Fox LLP
1050 Connecticut Avenue
Washington, DC 20036, USA
Attention: John Dwyer, Esq.

Notices to BioLine Innovations Jerusalem L.P. shall be addressed to:

BioLine Innovations Jerusalem L.P.
19 Hartum Street
P.O. Box 45158
Jerusalem 91450, Israel
Attention: Chief Executive Officer

with copy to:

Arent Fox LLP
1050 Connecticut Avenue
Washington, DC 20036, USA
Attention: John Dwyer, Esq.

Any Party may change its address by giving notice to the other Party in the manner herein provided. Any notice required or provided for by the terms of this Agreement shall be in writing and shall be (a) sent by registered or certified mail, return receipt requested, postage prepaid, (b) sent via a reputable international courier service, (c) sent by facsimile transmission, or (d) personally delivered, in each case properly addressed in accordance with the paragraph above. The effective date of notice shall be the actual date of receipt by the Party receiving the same.

Section 10.7 Force Majeure. No failure or omission by a Party in the performance of any obligation of this Agreement shall be deemed a breach of this Agreement or create any liability if the same shall arise from any cause or causes beyond the control of such Party, including the following: acts of God; fire; storm; flood; earthquake; accident; war; rebellion; insurrection; riot; and invasion (each such event, a "Force Majeure Event") and provided that such Party cures such

failure or omission resulting from one of the above causes as soon as is practicable after the occurrence of one or more of the above-mentioned causes.

Section 10.8 Independent Contractors. It is understood and agreed that the relationship between the Parties hereunder is that of independent contractors and that nothing in this Agreement shall be construed as authorization for either BioLineRx or Ikaria to act as agent for the other.

Section 10.9 Limitations of Liability. NEITHER PARTY SHALL BE LIABLE FOR ANY INDIRECT, INCIDENTAL, CONSEQUENTIAL, SPECIAL, EXEMPLARY OR PUNITIVE DAMAGES ARISING OUT OF THIS AGREEMENT OR THE EXERCISE OF ITS RIGHTS HEREUNDER, OR FOR LOST PROFITS ARISING FROM OR RELATING TO ANY BREACH OF THIS AGREEMENT, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES. NOTHING IN THIS SECTION 10.9 IS INTENDED TO LIMIT OR RESTRICT (A) THE INDEMNIFICATION RIGHTS OR OBLIGATIONS OF EITHER PARTY WITH RESPECT TO THIRD PARTY CLAIMS; (B) ANY LOSSES, INCLUDING LOST PROFITS, ARISING FROM ANY (I) BREACH OF A PARTY'S OBLIGATIONS WITH RESPECT TO THE OTHER PARTY'S CONFIDENTIAL INFORMATION, (II) BREACH BY BIOLINERX OF THE EXCLUSIVE RIGHTS GRANTED IN SECTION 2.1 OR THE COVENANT CONTAINED IN SECTION 2.2, OR (III) USE OF ANY PATENT RIGHTS OR KNOW-HOW LICENSED HEREUNDER BEYOND THE SCOPE OF SUCH LICENSE; OR (C) ANY LOSSES ARISING AS A RESULT OF A PARTY'S FRAUD, GROSS NEGLIGENCE OR WILLFUL MISCONDUCT.

Section 10.10 No Implied Waivers; Rights Cumulative. No failure on the part of BioLineRx or Ikaria to exercise, and no delay in exercising, any right, power, remedy or privilege under this Agreement, or provided by statute or at law or in equity or otherwise, shall impair, prejudice or constitute a waiver of any such right, power, remedy or privilege or be construed as a waiver of any breach of this Agreement or as an acquiescence thereto, nor shall any single or partial exercise of any such right, power, remedy or privilege preclude any further or other exercise thereof or the exercise of any other right, power, remedy or privilege.

Section 10.11 Severability. If, under applicable law or regulation, any provision of this Agreement is invalid, incomplete or unenforceable, or otherwise directly or indirectly affects the validity of any other material provision(s) of this Agreement (such invalid, incomplete or unenforceable provision, a "Severed Clause"), this Agreement shall endure except for the Severed Clause. The Parties shall consult one another and use reasonable efforts to agree upon a valid, complete and enforceable provision that is a reasonable substitute for the Severed Clause in view of the intent of this Agreement.

Section 10.12 Execution in Counterparts; Facsimile Signatures. This Agreement may be executed in counterparts, each of which, when so executed and delivered, shall be deemed to be an original, and all of which, taken together, shall constitute one and the same instrument even if both Parties have not executed the same counterpart. Signatures provided by facsimile transmission shall be deemed to be original signatures.

REMAINDER OF PAGE LEFT EMPTY; NEXT PAGE IS THE SIGNATURE PAGE

IN WITNESS WHEREOF, the Parties have executed this License and Commercialization Agreement as of the Effective Date.

IKARIA DEVELOPMENT SUBSIDIARY ONE LLC

By: /s/ Matthew M. Bennett

Name: Matthew M. Bennett

Title: Senior Vice President

BIOLINERX LTD.

By: /s/ Morris Laster M.D.

Name: Morris Laster M.D.

Title: CEO

BIOLINE INNOVATIONS JERUSALEM L.P.
by its General Partner, BioLine Innovations Jerusalem, Ltd.

By: /s/ Morris Laster M.D.

Name: Morris Laster M.D.

Title: Director

SCHEDULE 1.30

PROTOCOL FOR ON-GOING PHASE I/II TRIAL

[*PROTOCOL IMMEDIATELY FOLLOWS*]

CLINICAL STUDY

Protocol No. BL-1040.01
Version 5.00 Incorporating Amendments 1, 2, 3 and 4
Safety and Feasibility
Final

A Phase I, multi-center, open label study designed to assess the safety and feasibility of the injectable BL-1040 implant to provide scaffolding to infarcted myocardial tissue

BioLine Innovations Jerusalem

Confidentiality Statement

Annotated Protocol incorporating Amendment 1, Amendment 2, Amendment 3, and Amendment 4
01 December 2008

PROTOCOL NUMBER:	BL-1040.01 Safety and Feasibility
DATE OF PROTOCOL:	Final, **01 December** 2008 Version 2 incorporating Amendment 1, 07 August 2007 Version 3 incorporating Amendment 2, 03 December 2007 Version 4 incorporating Amendment 3, 17 April 2008 **Version 5 incorporating Amendment 4, 27 November 2008**
PROTOCOL TITLE:	A Phase I, multi-center, open label study designed to assess the safety and feasibility of the injectable BL-1040 implant to provide scaffolding to infarcted myocardial tissue
SPONSOR:	BioLine Innovations Jerusalem

Responsible study personnel:

Name:	Prof. Moshe Phillip, MD, Vice-President of Medical Affairs, Sr. Clinical Advisor
Address:	BioLine Innovations Jerusalem, 19 Hartum St., POB 45158 Jerusalem, Israel 91450
Phone:	+972-2-548-9100
Fax:	+972-2-548-9101
e-mail:	moshep@biolinerx.com

Name:	Shmuel Tuvia, PhD
Address:	BioLine Innovations Jerusalem, 19 Hartum St., POB 45158 Jerusalem, Israel 91450
Phone:	+972-2-548-9100, ext. 124
Fax:	+972-2-548-9101
e-mail:	shmuelt@biolinerx.com

Name:	Moti Gal, Clinical Operations Manager
Address:	BioLine Innovations Jerusalem, 19 Hartum St., POB 45158 Jerusalem, Israel 91450
Phone:	+972-2-548-9100, ext. 147
Fax:	+972-2-548-9101
e-mail:	motig@biolinerx.com

Name:	Jonathan Leor, MD, Medical Advisor
Address:	Head, Neufeld Cardiac Research Institute. Tel-Aviv University Sheba Medical Center Tel-Hashomer, Israel 52621
Phone:	+972-3-534-8685, 972-3-530-2614
Fax:	+972-3-535-1139
e-mail:	leorj@post.tau.ac.il

CRO:	Venn Life Sciences AG
Address:	Elisabethenstrasse 23/3, CH- 4051 Basel
Phone:	+41 61 201 11 00Fax: +41 61 273 42 50

Authorized representative:	Voisin Consulting
Address:	3, rue des Longs Prés, 92100 Boulogne, France
Phone:	+33-1-41-31-8300
Fax:	+33-1 41-31-8309
e-mail:	voisin@voisinconsulting.com

Medical Monitor, US (ISMB support only)
Name: Sanjay Machado, MD
Address: Venn Life Sciences Group
7355 TransCanada Hwy
Suite 200
Saint-Laurent, Quebec, Canada H4T 1T3

Phone: +1 514.315.2992 ext 117
Fax: +1 514.315.0995
e-mail: sanjay.machado@vlsworldwide.com

Medical Monitor, Europe
Name: Andrea Kempf-Mueller, MD
Address: Venn Life Sciences AG
Elisabethenstrasse 23/3, 4051 Basel, Switzerland
Phone: +41 61 201 11 83
Fax: +41 61 273 42 50
e-mail: andrea.kempf-mueller@vlsworldwide.com

Investigator's Signature Page

INVESTIGATOR:

Name:

Address:

Phone:
Fax:
e-mail:

I, the undersigned, have reviewed this Protocol, including Appendices, and I will conduct the clinical study as described and will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigator Brochure.

Date/Place _____ Signature _____
(Name of Investigator)

Sponsor Signature Page

Sponsor:	**BioLine Innovations Jerusalem**
Address:	**19 Hartum St., POB 45158**
	Jerusalem, Israel 91450
Phone:	**+972-2-548-9100**
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I have read the protocol and confirm that the protocol follows the current GCP guidelines.

Date/Place 27 Jan 2009 Signature /s/ Moshe Phillip
(Prof Moshe Phillip, VP of Medical Affairs, Sr. Clinical Advisor)

Date/Place 27 Jan 2009 Signature /s/ Shmuel Tuvia
(Shmuel Tuvia, PhD, Project Manager)

Date/Place 27 Jan 2009 Signature /s/ Moti Gal
(Moti Gal, Clinical Operations Manager)

Medical Advisor Signature Page

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I have read the protocol and confirm that the protocol follows the current GCP guidelines.

Date/Place 28/1/09

Signature /s/ Jonathan Leor
(Jonathan Leor, MD, Medical Advisor)

Synopsis

STUDY NUMBER	BL-1040.01
TITLE OF THE STUDY	A Phase I, multi-center, open label study designed to assess the safety and feasibility of the injectable BL-1040 implant to provide scaffolding to infarcted myocardial tissue
STUDY CENTER/COUNTRY	Approximately **10** centers in 3 countries: ~~Netherlands~~, Belgium, Germany, ~~Israel~~, possibly Switzerland
PLANNED STUDY PERIOD + CLINICAL PHASE	Q1 2008 to **Q1 2010** Phase I
INDICATION AND RATIONALE	Heart failure after myocardial infarction (MI) is often precipitated by early and progressive extracellular matrix degradation and pathological remodeling of the left ventricle (LV). In response to MI, a series of molecular, cellular and physiological responses are triggered, which can lead to early infarct expansion (infarct thinning), which may result in early ventricular rupture or aneurysm formation and the transition to heart failure. Late remodeling involves the left ventricle globally and is associated with time-dependent dilatation, and the distortion of ventricular shape. The failure to normalize increased wall stresses results in progressive dilatation, recruitment of border zone myocardium into the infarct, and deterioration in contractile function. Current anti-remodeling therapies are clearly limited, as many ventricles continue to enlarge and mortality and morbidity remain significantly high. Based on the mechanism of LV remodeling, it has been hypothesized that injection of biomaterials into the infarct could thicken the infarct, arrest infarct expansion, prevent LV dilatation and reduce wall stress that initiates progressive adverse LV remodeling. BL-1040 Myocardial Implant is a non-pharmacologic cross-linked alginate solution administered via intracoronary (IC) injection to infarcted tissue, forming a flexible, three-dimensional mechanical scaffold. BL-1040 Myocardial Implant presents a novel, safe and non-surgical therapy that directly addresses the stability and structural integrity of myocardial tissue while potentially preventing post infarction remodeling, primarily via limiting left ventricle dilation.
OBJECTIVES	• To evaluate the safety of the BL-1040 myocardial implant in patients after MI at high risk for LV remodeling and CHF. • To provide feasibility data in order to initiate and conduct a pivotal clinical study evaluating the safety and efficacy of the BL-1040 implant in patients following myocardial infarction.

ENDPOINTS	Primary safety endpoints
	Occurrence of all adverse events including but not limited to
	• All MIs
	• Cardiovascular hospitalization
	• Serious ventricular arrhythmias sustained:
	  • VT (symptomatic or sustained VT [duration longer than 30 seconds or 100 beats, or associated with hemodynamic collapse])
	  • VF
	  • symptomatic bradycardia, pauses of longer than 3.0 seconds, complete atrioventricular block, Mobitz II atrioventricular block
	• Symptomatic heart failure (NYHA criteria + physical examination OR hospitalization due to heart failure)
	• Renal failure
	• Stroke
	• Death

	Secondary safety endpoints • Change from baseline in LV dimensions (end-systolic volume index, end-diastolic volume index, left ventricular mass) • Change from baseline in regional (infarct related) and global wall motion score • Change from baseline in ejection fraction • Cardiac rupture • NT-proBNP	
DESIGN	Multi-center, open label	
PATIENTS	NUMBER	Maximum 30
	MAIN INCLUSION CRITERIA	• Signed informed consent • 18 to 75 years of age, inclusive • Male or female • Negative pregnancy test for women of child-bearing potential, or surgically sterile, or post menopausal • Acute MI defined as: 1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms: b) development of pathologic Qwaves on the ECG: c) ECG changes indicative of ischemia (ST segment elevation or depression) 2. First anterior or inferolateral STEMI or Qwave MI (QMI Anterior: V1-V3 or V1-V4 or V1-V5 or V1-V6.QMI Inferior: L2, L3, AVF, or L2, L3, AVF+ V5, V6 or L2, L3, AVF+ V6-V9 [posterior leads]) 3. Regional wall motion score index (at least 4 out of 16 akinetic segments) • One or more of the following: • LVEF >20% and <45% measured and calculated by 2-dimensional measurement • Biomarkers: peak CK > 2000 IU • Infarct size > 25% as measured by MRI • Successful revascularization with PCI ~~with 1 stent only~~, within 7 days of the index MI (only safe and MRI compatible stents) • At time of application of study device, patient must have patent infarct related artery (IRA) and TIMI flow grade = 3
	MAIN EXCLUSION CRITERIA	• History of CHF, Class I to Class IV, as per NYHA criteria • History of prior LV dysfunction • At time of application of study device - Killip III-IV (pulmonary edema, cardiogenic shock - hypotension [systolic < 90 mmHg] and evidence of peripheral hypoperfusion [oliguria, cyanosis, sweating]) or HR > 100 bpm • Patient with pacemaker • Prior CABG • Prior MI • History of stroke • Significant valvular disease (moderate or severe) • Patient is a candidate for CABG or PCI on non-IRA • Patient is being considered for CRT within the next

		30 days • Renal insufficiency (eGFR < 60) • Chronic liver disease (> 3 times upper limit of normal) • Life expectancy < 12 months • Current participant in another clinical trial, or participation in another trial within the last 6 months • Any contraindication to coronary angiography, MRI or PCI procedures • Patient taking anti-coagulation medication prior to MI • Pregnant or lactating women; pregnancy confirmed by urine pregnancy test
STUDY DEVICE	ROUTE OF APPLICATION	Administered via intracoronary (IC) injection, using multiple commercially available devices
	DURATION AND FREQUENCY	2 mL of BL-1040 administered for no longer than **30** seconds
	FORMULATION	Calcium D-Gluconate (Gluconic acid hemicalcium salt) PRONOVA UP VLVG (Generic name: Sodium Alginate) Water for Injection USP/EP
SAFETY EVALUATIONS		
TIMING AND ASSESSMENTS PERFORMED		Screening • 1st Coronary angiography, PCI and stent (as part of treatment of MI) • Physical examination • Vital signs • 12-lead ECG • Blood and urine sampling for laboratory safety parameters (biochemistry, hematology and urinalysis) • Total CK/CK MB • NT-proBNP • Mandatory echocardiography; MRI as an additional measurement is encouraged Telephone contact, 1 week post-procedure • Phone call to confirm status of patient discharged from the hospital Day 1 and during hospitalization • Physical examination daily during hospitalization • Vital signs daily during hospitalization • 12-lead ECG prior to and after administration of BL-1040; daily during hospitalization • 24 hour Holter monitor (after completion of 12-lead ECG) • Blood and urine sampling for laboratory safety parameters (biochemistry, hematology and urinalysis), on Day 1 (only if not done within the previous 48 hours) and on day of discharge (only if not done within the previous 48 hours) • Total CK/CK MB measured prior to, and 8, 16, 24 and 48 hours after administration of BL-1040 • NT-proBNP on Day 1 (only if not done within the previous 48 hours) and on day of discharge (only if not done within the previous 48 hours) • continuous ECG during the procedure • 2nd cardiac catheterization (for implantation of BL-1040) • PTT or ACT measurements, during procedure only (prior to implantation of BL-1040 and prior to removal of sheath)

	Follow-up visits (Days 30, 90 180 [End of Study]; Months 12, 24, 36, 48 and 60) • Physical examination • Vital signs • 12-lead ECG • 24 hour ambulatory Holter monitoring • Blood and urine sampling for laboratory safety parameters (biochemistry, hematology and urinalysis) • NT-proBNP (through Day 180 only) • Mandatory echocardiography: MRI as an additional measurement is encouraged (MRI through Day 180 only) • Minnesota Living with Heart Failure® questionnaire AEs and SAEs will be collected throughout the study
PROCEDURE	Patient is admitted to the hospital as a result of an AMI. As part of the inclusion criteria for this study, the patient will undergo revascularization with PCI stent implantation. Within 7 days of the index MI, the patient will undergo an echocardiogram to determine LVEF. Although not mandatory, the patient will be encouraged to undergo an MRI as an additional assessment. If the patient satisfies inclusion/exclusion criteria, a 2nd cardiac catheterization will be performed to administer BL-1040 after revascularization but within 7 days of the index AMI. BL-1040 is applied via intracoronary injection through the infarct related artery. Patients discharged from the hospital will be contacted by phone on Day 8 for a safety follow-up. Follow-up examinations are scheduled for Day 30, Day 90 and Day 180 (End of Study) post-procedure. In addition, the patient will return to the hospital at Months 12, 24, 36, 48 and 60 for yearly follow-up assessments, as part of a long-term safety follow-up.
STATISTICAL METHODS	All data recorded will be presented in data listings and summary tables, as appropriate. Missing values will not be replaced. No formal hypothesis testing will be performed. All participants who received BL-1040 will be included in the safety analysis. Any excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be finalized prior to database lock. Continuous variables (age, height, weight) will be summarized using mean, median, standard deviation, minimum, maximum, and number of available observations. Qualitative variables will be summarized by counts and percentages. An interim safety analysis will be performed after 5 patients have completed the Day 30 visit, on all data collected up to this timepoint.

Schedule of Events

Visits/Week	Hospitalization				Post discharge follow-up				
Study days	Screening (Day) (-7) to Day (-1)	Day 1 Day of application(1)	Daily during hospitalization(2)	Day of discharge	Telephone Contact Day 8 (± 1 day)	Day 30 (± 5 days)	Day 90 (± 5 days)	Day 180 (± 7 days) End of Study Visit	Follow-up Safety Visits (Months 12, 24, 36, 48 60, ± 30 days)
AMI	X								
Hospitalization	X	X	X	X	X				
Coronary angiography, PCI, stent(1)	X								
Informed consent	X								
Inclusion/exclusion criteria	X								
Pregnancy test	X								
Demography; medical history; concurrent illnesses	X								
Physical examination	X	X	X	X		X	X	X	X
Vital signs (temperature, arterial BP, weight)	X	X	X	X		X	X	X	X
12-lead ECG	X	X(4)	X	X		X	X	X	X
Laboratory safety parameters	X(5)	X(6)		X(6)		X	X	X	X
Total CK/CK MB	X	X(7)							
NT-proBNP	X	X(6)		X(6)		X	X	X	
Echocardiography/MRI	X					X	X	X	X
Continuous ECG monitoring		X(9)							
Cardiac catheterization; application of BL-1040; coronary angiography		X							
PTT or ACT measurements		X(10)							
24-hour ambulatory Holter monitoring		X				X	X	X	X
Safety contact for discharged patients					X				
Minnesota Living with Heart Failure						X	X	X	X
Serious/Adverse events and concomitant medication	X	X	X	X	X	X	X	X	X

(1) Device to be administered within 7 days of AMI
(2) Patient must remain hospitalized for at least 48 hours after procedure.
(3) Done as treatment of AMI
(4) Prior to and after administration of BL-1040
(5) Troponin I or T to be measured at Screening only
(6) If not done within previous 48 hours
(7) Parameters to be assessed prior to, and 8, 16, 24 and 48 hours after administration of BL-1040
(8) Echocardiography to be done at each visit. MRIs are to be encouraged as an additional assessment through Day 180, but are contingent upon patient agreement. MRIs are not to be requested as part of the Follow-up Safety visits.
(9) Patient to be connected prior to implantation of BL-1040, and for the duration of the procedure
(10) Measured prior to implantation of BL-1040, and prior to removal of sheath

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List of Abbreviations

AE(s)	Adverse event(s)
ALT	Alanine transminase
AMI	Acute myocardial infarction
AST	Aspartate transaminase
BP	Blood pressure
bpm	Beats per minutes
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CHF	Chronic heart failure
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CV	Cardiovascular
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EOS	End of study
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HPF	High power field
HR	Heart rate
IC	Intracoronary
ICH	International Conference on Harmonization
IRA	Infarct related artery
ISMB	Independent Safety Monitoring Board
LDH	Lactate dehydrogenase
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
min	Minute
mL	Milliliter
MRI	Magnetic resonance imaging
NCE	New chemical entity
NT-proBNP	N-terminal prohormone brain natnuretic peptide
NYHA	New York Heart Association
°C	Degrees centigrade
OTC	Over the Counter
PCI	Primary coronary intervention
QMI	Qwave myocardial infarction
SAE(s)	Serious Adverse Event(s)
SAS	Statistical Analysis System
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
VF	Ventricular fibrillation
VT	Ventricular tachycardia

1 Introduction

1.1 Background

1.1.1 Acute Myocardial Infarction- Definition

Acute myocardial infarction (AMI) is defined as death or necrosis of myocardial cells. It is a diagnosis at the end of the spectrum of myocardial ischemia or acute coronary syndromes. AMI occurs when myocardial ischemia exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms that are designed to maintain normal cardiac function. Ischemia at this critical threshold level, when present for an extended time period, results in irreversible myocardial cell damage and cell death.

1.1.2 Infarction types and pathogenesis

Critical myocardial ischemia may arise as a result of increased myocardial metabolic requirement and/or reduction in the delivery of oxygen and nutrients to the myocardium through the coronary circulation, or both. An interruption in the supply of myocardial oxygen and nutrients occurs when blood flow to the myocardium is interrupted by occlusion of a coronary artery. Often, this event is caused by a thrombus superimposed on an ulcerated or unstable atherosclerotic plaque that left untreated for as little as a 20-40 minutes, can lead to irreversible cell damage and cell death. A high-grade (> 75%) permanent coronary artery stenosis due to atherosclerosis or a dynamic stenosis coupled with coronary vasospasm can also reduce the supply of oxygen and nutrients and be a factor involved in AMI. Additional cardiac valvular pathologies and low cardiac output states associated with a decreased aortic diastolic pressure, which is the prime component of coronary perfusion pressure, can also precipitate AMI.

1.1.3 Mechanisms of myocardial damage

The severity of an AMI is dependent on three factors: the level of the occlusion in the coronary artery, the length of time of the occlusion, and the presence or absence of collateral circulation. In general, the more proximal the coronary occlusion, there is a greater risk of an increased area of necrosis. The larger the AMI, the chance of death due to a mechanical complication or pump failure increases. In addition, the longer the time period of vessel occlusion, there is a greater chance of irreversible myocardial damage distal to the occlusion.

The death of myocardial cells first occurs in the area of myocardium that is most distal to the arterial blood supply, the endocardium. As the duration of the occlusion increases, the area of myocardial cell death enlarges, extending from the endocardium to the myocardium and ultimately to the epicardium. The area of myocardial cell death then spreads laterally to areas of watershed or collateral perfusion. The extent of myocardial cell death defines the magnitude of the AMI. If blood flow can be restored to at-risk myocardium, more heart muscle can be saved from irreversible damage or death. The ischemic zone will undergo inflammatory necrotic changes, and the myocardial tissue will eventually be completely replaced by fibrous infarct tissue. In the early stages after an AMI, the damage causes deterioration of cardiac muscle contractility and structural integrity. This results in thinning of the walls of the heart, which can have severe consequences including rupture at the site, expansion of the area of damage, and the formation of blood clots. After some weeks or months, this can evolve to dilatation of the heart, which further reduces its ability to pump blood efficiently, resulting in heart failure.

1.1.4 Treatment of AMI

The goal of treatment for AMI is early reperfusion by rapid revascularization of the occluded culprit coronary artery both by medical means to dissolve the clot with thrombolytics or by cardiac catheterization with primary coronary intervention (PCI) and deployment of stents to

maintain patency of the culprit coronary artery. However, while re-opening of the culprit coronary vessel can prevent the development of a large AMI and prevent further loss of viable myocardium, it does not affect myocardial tissue that has already undergone irreversible damage. An undeniable adverse outcome of AMI is progressive worsening of ventricular function that, if left unattended, culminates in the syndrome of congestive heart failure. To date, no treatment has been developed to reliably prevent the deterioration of ventricular function that follows a large AMI. Treatment options for AMI and for the resulting heart failure include medical management, heart transplantation. mechanical circulatory assist devices (left ventricular assist device, etc.), and surgical ventricular restoration, all of which have specific limitations.

1.2 Rationale and justification

BL-1040 Myocardial Implant presents a novel, safe and non-surgical therapy that directly addresses the stability and structural integrity of myocardial tissue in this patient population. BL-1040 potentially prevents post infarction remodeling primarily via limiting left ventricle (LV) dilation, while the untreated patient LV will continue to dilate or enlarge. BL-1040, by creating a scaffold, may stabilize the AMI and limit post AMI expansion manifested as LV dilation.

There are currently no other available medical and/or surgical interventions that directly address the stability and structural integrity of myocardial tissue damaged as a result of AMI. In the setting of an AMI, an inflammatory response triggers the degradation of the extracellular matrix, thus weakening of the collagen cross-link structure or structural “backbone” of the myocardium. Degradation of the extracellular matrix leads to infarct expansion manifested by myocardial wall thinning and often, aneurysmal dilation with subsequent ventricular enlargement. This process results in progressive LV remodeling and increased LV wall stress. The latter can increase myocardial oxygen consumption, a condition that the infarcted and/or failing LV can ill afford and one that can contribute to increased long-term mortality and morbidity.

LV dilation is the predominant cause for morbidity and mortality in congestive heart failure [2], demonstrated that patients with LV end systolic volume smaller than 95 mL showed a 94 % survival after 5 years while LV patients with LV end systolic volume greater than 130 mL showed a 52 % survival after 5 years. Both diastolic and systolic were the main predictors for mortality. Patients with end-stage ischemic heart failure presenting dilated LV with an akinetic/dyskinetic region over 35% and with left ventricular end systolic index >60 mL/m2 are offered LV reconstruction or surgical ventricular restoration (SVR) in order to reduce LV volume and to restore normal LV shape. Overall, in a large number of studies performed using SVR, there is strong evidence that SVR is safe and effective, showing significant reduction in mortality and readmission levels together with significant improvement in ejection fraction as well as in LV end systolic/diastolic index.

2 Study Objectives

The objectives of this study are:

- to evaluate the safety of the BL-1040 myocardial implant in patients after MI at high risk for LV remodeling and CHF, and
- to provide feasibility data in order to initiate and conduct a pivotal clinical study evaluating the safety and efficacy of the BL-1040 implant in patients following myocardial infarction.

3 Safety Endpoints

3.1 Primary endpoints

Primary safety endpoints include:

- occurrence of all adverse events including but not limited to
  - all MLs
  - cardiovascular hospitalization
  - serious ventricular arrhythmias sustained
    - VT (symptomatic or sustained VT [duration longer than 30 seconds or 100 beats, or associated with hemodynamic collapse])
    - VF
    - symptomatic bradycardia, pauses of longer than 3.0 seconds, complete atrioventricular block, Mobitz II atrioventricular block
  - symptomatic heart failure (NYHA criteria + physical examination OR hospitalization because of heart failure)
  - renal failure
  - stroke
  - death

3.2 Secondary endpoints

Secondary safety endpoints include:

- change from baseline in LV dimensions (end-systolic volume index, end-diastolic volume index, left ventricular mass)
- change from baseline in regional (infarct related) and global wall motion score
- change from baseline in ejection fraction
- cardiac rupture
- NT-proBNP

4 Investigational Plan

4.1 Summary of study design

This is an open label, multi-center, sequentially enrolled. Phase I study to assess the safety and feasibility of the injectable BL-1040 myocardial implant to provide scaffolding to infarcted myocardial tissue.

Patients who experience an MI will be admitted to the hospital. As part of the treatment for the MI, patients will undergo PCI and stent implantation. Patients will also undergo an echocardiography (and if they agree, an MRI) to determine the extent of damage to the infarct related artery (IRA). Patients who satisfy inclusion/exclusion criteria will be enrolled into the study. The BL-1040 myocardial implant will be injected into the IRA, distally to the implanted stent.

The first 2 patients will be sequentially enrolled. After both patients have completed Day 30 assessments, and after approval by the Independent Safety Monitoring Board (ISMB), the decision will be made to enroll 3 additional patients. After the ISMB reviews the Day 30 assessments of these patients, the decision will be made to enroll a maximum of 25 additional patients. Details are provided in Sec. 4.2.

Both female and male patients must agree to use effective contraception (as agreed with the Investigator) for 6 months (180 days) after the procedure.

4.1.1 Estimated study duration

The study is planned to last from Q1 2008 to **Q1 2010**. The clinical study phase is **180** days for each patient. A long term safety follow-up will include visits at Months 12, 24, 36, 48, and 60. Patients will be consented for the entire 5 year period.

4.1.2 Number of Patients

The maximum number of patients enrolled in this study will be 30.

4.2 Sequential enrollment

The first 2 patients will be sequentially enrolled into the study. After the 1st patient has completed Day 30 assessments, the Independent Safety Monitoring Board (ISMB, Sec. 4.3) will review the patient's data through Day 30. The ISMB will then decide whether to give approval to enroll the 2nd patient. After the 2nd patient has completed Day 30 assessments, the ISMB will again review the data and provide approval for enrollment of the next 3 patients. After all 3 patients have completed Day 30 assessments, the ISMB will review the data from these patients and provide approval for opening enrollment to the balance of the patients (maximum of 25).

4.3 Responsibilities of the Independent Safety Monitoring Board

An Independent Safety Monitoring Board (ISMB) will be established prior to the start of the study to monitor the safety of BL-1040 during the conduct of the protocol. This ISMB will consist of physicians with expertise in cardiovascular disease, particularly in the area of coronary artery disease and with experience monitoring safety of drugs and/or devices for cardiovascular applications, and will have no participation in the trial in any other capacity.

The ISMB will ensure that this study meets the highest standards of patient safety. During the study the ISMB will have the following main responsibilities:

- review 30 day safety data patients from the first 2 sequentially enrolled patients to determine whether 3 additional patients may be enrolled: after reviewing the 30 day safety data from these 3 patients, will determine whether the balance of patients may be enrolled
- within 30 days of enrolment of each successive group of 5 patients receiving the device, will review all SAEs occurring to date and will recommend continuation, discontinuation, or modification of the procedure or protocol, based on a determination of whether the occurrence of serious, unexpected, or device-related adverse events (Sec. 7) might outweigh the potential benefit achievable with the device
- review emerging findings in patients and identify potential safety concerns with BL-1040
- will receive information, on an expedited basis, on all Serious Adverse Events (SAEs), clinically significant laboratory values/vital signs, ECG abnormalities and data from patients who decided to prematurely discontinue the study. All SAES that occur in the cath lab during or after the procedure to administer BL-1040 should be reviewed promptly by the ISMB. The ISMB will review this information and may decide to interrupt, alter, or terminate the trial
- will adjudicate whether or not an event is unexpected, based on a pre-specified list of expected SAEs within the study population.

4.3.1 Stopping Criteria

Given the uncontrolled nature of the study, and the small sample size, it is not practical to provide a quantitative stopping rule.

Moreover, given the severely ill nature of the patients who will be enrolled in the study (those with large myocardial infarction and substantial LV dysfunction), adverse cardiac outcomes, including fatal ones, are to be expected in this population, regardless of participation in the study.

The study will be stopped when any of the following occur:

1. Completion of the study
2. ISMB and sponsor judge that the study treatment appears to be unsafe for patients. The ISMB will make this assessment based not only upon the frequency of observed complications, but also upon the character and qualitative nature of the events. This determination will be made in the context of clinical judgement of experienced cardiologists regarding the expected outcome in this population of patients and whether observed outcomes differ substantively from the expectation. The committee reserves the right to stop the study after analysis of outcomes of sequential procedures. A decision to stop will be considered by the ISMB in the event of occurrence of severe, unusual or unexpected events.
3. The ISMB may consider putting the trial on hold or terminating it and will base it decision on weighing the balance between potential but hypothetical benefits and possible risks to the participants in the study.

4.4 Inclusion criteria

The inclusion criteria for this study are:

- voluntarily signed the informed consent form prior to the conduct of any study specific procedures
- male or female inpatients aged 18 to 75, inclusive

- negative pregnancy test for all women of child-bearing potential, or surgically sterilized (i.e. tubal ligation, hysterectomy) prior to Screening, or post-menopausal for at least 1 year
- acute MI defined as:
    - typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms; b) development of pathologic Qwaves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression)
    - first anterior or inferolateral STEMI or Qwave MI (QMI Anterior: V1-V3 or V1-V4 or V1-V5 or V1-V6.QMI Inferior: L2, L3, AVF, or L2, L3, AVF+ V5, V6 or L2, L3, AVF+ V6-V9 [posterior leads])
    - regional wall motion score index (at least 4 out of 16 akinetic segments)
- one or more of the following:
    - LVEF >20% and <45% measured and calculated by 2-dimensional measurement
    - Biomarkers: peak CK > 2000 IU
    - infarct size > 25% as measured by MRI
- successful revascularization with PCI within 7 days of the index MI (only safe and MRI compatible stents)
- at time of application of device patient must have patent infarct related artery (IRA) and TIMI flow grade = 3

4.5 Exclusion criteria

Exclusion criteria for this study are:

- history of CHF, Class I to Class IV, as per NYHA criteria
- history of prior LV dysfunction
- at time of application of study device - Killip III-IV (pulmonary edema, cardiogenic shock - hypotension (systolic < 90 mmHg) and evidence of peripheral hypoperfusion (oliguria, cyanosis, sweating) or HR > 100 bpm
- patient with pacemaker
- prior CABG
- prior MI
- history of stroke
- significant valvular disease (moderate or severe)
- patient is a candidate for CABG or PCI on non-IRA
- patient is being considered for CRT within the next 30 days
- renal insufficiency (eGFR < 60)
- chronic liver disease (> 3 times upper limit of normal)
- life expectancy < 12 months
- current participant in another clinical trial, or participation in another trial within the last 6 months
- any contraindication to coronary angiography, MRI or PCI procedures
- patient taking anti-coagulation medication prior to MI
- pregnant or lactating women; pregnancy confirmed by urine pregnancy test
- patients with a reasonable likelihood for non-compliance with the protocol
- any other reason that, in the Investigator's opinion, prohibits the inclusion of the patient into the study

4.6 Withdrawal criteria during the study

Each patient has the right to withdraw from the trial at any time for any reason.

The Investigator must make at least 3 documented attempts to contact those patients who do not return for the scheduled follow-up visits. Attempts must be recorded in the patient's file.

The Sponsor reserves the right to terminate the study at any time.

Upon withdrawal from the study any time after administration of study device, the patient will undergo the End of Study assessments (Section 6.2.1.5: Table 6.1).

Dropouts that occur after implantation of BL-1040 will not be replaced.

4.7 Treatment allocation

This is an open label study. All patients will be treated with BL-1040. Patient eligibility will be established prior to treatment with BL-1040.

If a patient discontinues from the study, the patient number will not be reused.

4.8 Method of blinding and unblinding

As this is an open label study, there will be no blinding or unblinding procedure.

5 Product Overview

5.1 BL-1040

BL-1040 myocardial implant is a non-pharmacologic, non-surgical, cross-linked alginate solution administered via intracoronary (IC) injection to infarcted tissue. BL-1040 completely disintegrates into its constituent polymers within approximately 90 days after deposition, and is excreted in the urine.

5.2 Formulation

The formulation of BL-1040 is shown in Table 5.1.

Table 5.1 Formulation of BL-1040

0.3% Calcium D-Gluconate (Gluconic acid hemicalcium salt)	Sigma, Dr. Paul Lohmann GmbH KG
1% PRONOVA UP VLVG Generic name: Sodium Alginate	FMC BioPolymer/ NovaMatrix
Water for Injection USP/EP	

5.3 Dosage and application

BL-1040 will be administered to the coronary vasculature using multiple commercially available devices. Table 5.2 provides a list of the commercially available components that will be required in order to delivery the BL-1040 implant.

Table 5.2 List of Commercially Available BL-1040 Delivery Devices

BL-1040 Implant Delivery Devices

1 Standard endovascular sheath (femoral or radial or brachial)
2 Standard coronary guiding catheter (example — Launcher, ref LA6AR10SH)
3 Guidewire 0.014 inch (example - Boston Scientific, ref. 383931-035J)
4 Torque device (example - Boston Scientific, ref. K903606))
5 Guidewire introducer (example Input Ref. 87311)
6 Microcatheter designed for coronary intravascular use such as multipurpose probing endovascular microcatheter. Example:(Boston Scientific Catalog number SCH 50058) or Transit microcatheter, (Cordis Endovascular Systems, MiMI Lakes, Fla.) or Renegase Hi-Flo microcatheter (Boston Scientific)
7. Disposable syringe, Intmed 5 mL sterile CE, ISO9001, ISO13488

Cardiac catheterization should be done according to the guidelines of the American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on Cardiac Catheterization Laboratory Standards. All angiographies will be evaluated by a core laboratory. BL-1040 is delivered intra-coronary (IC) via a microcatheter that is intended for coronary intravascular use.

The timing of BL-1040 administration is within 7 days after the index MI. Two (2) mL of BL-1040 will be injected IC through the infarct related artery supplying the infarcted area. BL-1040 may not be mixed with any contrast medium.

All patients will be treated in the same manner.

Detailed instructions for the application of BL-1040 are provided in a separate Instruction Manual.

5.4 Labelling/Packaging

BL-1040 will be packed in a sterile cylindrical injection vial, type A glass. Vials are filled with sterile BL-1040 and sealed with a 20 mm rubber stopper, spun-on aluminum seal and a flip-off top.

All packages will be labeled according to the GMP guideline Volume 4, Annex 13 Manufacture of Investigational Medicinal Products (July 2003 Revision 1) [**1**] and local laws.

BL-1040 will be packed in labeled boxes, with at least the following information: study number, patient number, route of administration, storage guidelines, batch number, expiry date, instructions for administration, manufacturer name/code, and "Investigational use only".

The Sponsor must notify the Site Investigator, who has the overall responsibility for the study device, of the anticipated date of arrival.

5.5 Storage

The Site Investigator is responsible for ensuring that BL-1040 is stored in a safe refrigerated location (2-8° C) with controlled access. At this temperature, BL-1040 has a shelf life of 3 months. The temperature must be monitored once daily, and recorded on a temperature log.

BL-104 must be removed from the refrigerator and kept at room temperature 30 minutes prior to administration.

5.6 Compliance

BL-1040 will be administered by the Investigator only, and will not be dispensed to the patient or any other personnel.

5.7 BL-1040 accountability

Under no circumstances is it permitted to use study supplies for any purposes other than those specified in the protocol.

The Investigator will be provided with forms to enable accurate recording of all investigational product at all times. The Investigator must sign a statement that he/she has received BL-1040 for the study. At any time the figures of supplied, used and remaining BL-1040 must match. At the end of the study, it must be possible to reconcile delivery records with those of used and unused stocks. Account must be given of any discrepancies.

At the end of the study, all unused BL-1040 supplies and empty containers must be returned to the Sponsor.

5.8 Concomitant medication

The following medications may only be administered as indicated:

- ceftriaxone may not be administered during the 48 hours immediately prior to the administration of BL-1040, and for the 48 hours immediately following administration of BL-1040
- calcium solutions may not be administered during the first week of the study

The introduction of any medication not allowed by the protocol at any point in the study will require a discussion between the Investigator and the Sponsor. If, in the opinion of the Investigator, it becomes necessary to administer any medication during the study, the

Investigator will determine the dose and time of intake, and document the medication(s) in the patient's CRF.

Patients must be instructed not to begin any new medication before consulting with the Investigator (unless required for emergency medical use). The patient must be instructed that this prohibition applies to over-the-counter products as well as prescription drugs.

All patients will receive optimal medical therapy according to the relevant, updated guidelines from the European Society of Cardiology [3,4,5]. Optimal therapy including aspirin, anticoagulation if indicated, angiotensin-converting-enzyme inhibition, beta-blockade, aldosterone antagonists, when appropriate, and lipid-lowering therapy, unless contraindicated. Clopidogrel therapy will be initiated before PCI and continued for 1 year after myocardial infarction [3].

6 Study Procedures

6.1 General study aspects

This is an open label, multi-center study to assess the safety and feasibility of the injectable BL-1040 myocardial implant to provide scaffolding to infarcted myocardium.

Patients will be admitted to the hospital for treatment of an acute myocardial infarction (AMI), to include angioplasty and implantation of a-stent/s. Within 7 days of successful revascularization, patients will undergo an echocardiogram for assessment of the extent of the changes to the heart, and to verify cardiac inclusion/exclusion criteria. MRIs are to be encouraged as an additional assessment, but are contingent upon the agreement of the patient. After the echocardiogram/MRI, but still within 7 days of the index AMI, patients will undergo a 2nd cardiac catheterization to administer BL-1040. Patients will remain hospitalized for at least 48 hours after the procedure.

The BL-1040 scaffold will be injected into one infarct related artery (IRA), distally to the implanted stent/s. Patients will undergo cardiac monitoring before, during and after the procedure: a 12-lead ECG will be done prior to and after administration of BL-1040; patients will be connected to a continuous ECG monitor and will have continuous hemodynamic measurements during the procedure; immediately after the completion of the 12-lead ECG, a Holter monitor will be placed and will remain connected for the following 24 hours.

Patients will undergo physical examinations, assessment of vital signs and an ECG daily during hospitalization; safety blood sampling will be done on the day of discharge.

Patients who have been discharged from the hospital will be contacted by phone on Day 8 to confirm the administration of any concomitant medications, general status of the patient, and any doctor visits since hospital discharge.

Patients will return for follow-up visits on Day 30, Day 90 and Day 180 (End of Study). Additional follow-up safety visits are planned for Months 12, 24, 36, 48 and 60. At each visit, patients will again undergo a physical examination with measurement of vital signs, ECG, blood sampling, echocardiography and completion of the Minnesota Living with Heart Failure questionnaire®. At each follow-up visit, the patients will be hooked up to a 24-hour ambulatory Holter monitor, which will be returned the following day. MRIs are to be encouraged through Day 180 as an additional assessment, but are contingent upon the agreement of the patient. MRIs are not to be requested as part of the long term safety visits.

Echocardiograms, ECGs, Holters, angiographies and MRIs, will be evaluated in a core laboratory.

The first 2 patients will be sequentially enrolled; if approved by the ISMB; 3 additional patients will be enrolled. After review and approval of the 30 day safety data from these 3 patients, the balance of patients may be enrolled. Details are provided in Sec. 4.2.

Both female and male patients must agree to use effective contraception (as agreed with the Investigator) for 6 months (180 days) after the procedure.

6.2 Outline of study procedures

All study procedures are outlined in the Schedule of Assessments below (Table 6.1). A more detailed description of the study procedures performed at each study stage/visit is given in the following sections.

Table 6.1 Schedule of Events

	Hospitalization				Post discharge follow-up				
Visits/Week Study days	Screening Day (-7) to Day (-1)	Day 1 Day of application(1)	Daily during hospitalization(2)	Day of discharge	Telephone Contact Day 8 (± 1 day)	Day 30 (± 5 days)	Day 90 (± 5 days)	Day 180 (± 7 days) End of Study Visit	Follow-up Safety Visits (Months 12, 24, 36, 48 60, ± 30 days)
AM1	X								
Hospitalization		X							
Coronary angiography, PCI, stent(1)	X								
Informed consent	X								
Inclusion/exclusion criteria	X								
Pregnancy test	X								
Demography medical history; concurrent illnesses	X								
Physical examination	X	X	X	X		X	X	X	X
Vital signs (temperature, arterial BP. weight)	X	X	X	X		X	X	X	X
12-lead ECG	X	X(4)	X	X		X	X	X	X
Laboratory safety parameters	X(5)	X(6)		X(6)		X	X	X	X
Total CK/CK MB	X	X(7)							
NT-proBNP	X	X(8)		X(6)		X	X	X	
Echocardiography/MRI	X					X	X	X	X
Continuous ECG monitoring		X(9)							
Cardiac catheterization; application of BL- 1040; coronary angiography		X							
PTT or ACT measurements		X(10)							
24-hour ambulatory Holler monitoring		X				X	X	X	X
Safety contact for discharged patients					X				
Minnesota Living with Heart Failure®						X	X	X	X
Serious/Adverse events and concomitant medication	X	X	X	X	X	X	X	X	X

(1) Device to be administered within 7 days of AMI
(2) Patient must remain hospitalized for at least 48 hours after procedure.
(3) Done as treatment of AMI
(4) Prior to and after administration of BL-1040
(5) Troponin I or T to be measured at Screening only
(6) If not done within previous 48 hours
(7) Parameters to be assessed prior to. and 8, 16, 24 and 48 hours after administration of BL-1040
(8) Echocardiography to be done at each visit. MRIs are to be encouraged as an additional assessment through Day 180, but are contingent upon patient agreement. MRIs are net to be requested as part of the Follow-up Safety visits.
(9) Patient to be connected prior to implantation of BL-1040, and for the duration of the procedure
(10) Measured prior to implantation of BL-1040, and prior to removal of sheath

6.2.1 Detailed description of study stages/visits

6.2.1.1 Screening, Day -7 to Day -1

Patients are admitted to the hospital for treatment of an AMI, prior to enrollment into the study. The treatment will include PCI with placement of a stent. After signing of Informed Consent, and prior to initiation of any study-related procedures, the following activities will be carried out:

- confirmation of inclusion/exclusion criteria
- negative pregnancy test for all women of child-bearing potential (as defined in Inclusion Criteria)
- demographics
- medical history
- physical examination
- vitals signs
- 12-lead ECG, in supine position
- blood and urine sampling for laboratory safety parameters (biochemistry, hematology and urinalysis)
- blood sampling for Total CK/CK MB
- blood sampling for NT-proBNP
- echocardiography
- MRI, if patient agrees
- concomitant medication record (all currently prescribed and over the counter medications must be recorded in the Case Report Form [CRF], with dose and reason for use)
- pre-device serious/adverse events

6.2.1.2 Day 1

BL-1040 must be implanted within 7 days of the index AMI; the day of implant will be considered Day 1 of the study. Prior to implantation, the following assessments will be carried out:

- physical examination
- vital signs
- 12-lead ECG
- blood and urine sampling for laboratory safety parameters (biochemistry [excluding troponin I or T], hematology, and urinalysis), if not done within the previous 48 hours
- Total CK/CK MB
- NT-proBNP, if not done within the previous 48 hours
- connection to continuous ECG monitoring

BL-1040 will be implanted in the infarcted tissue via the IRA, distally to the stent as outlined in the separate BL-1040 Instruction Manual. During the procedure the following assessments will be done:

- continuous ECG monitoring
- continuous hemodynamic measurements (arterial blood pressure)
- blood sampling for PTT or ACT, prior to implantation of BL-1040 and prior to removal of sheath

An additional coronary angiography will be done 3 minutes after implantation of the BL-1040, and will include an assessment of TIMI flow and myocardial blush.

The following assessments will be done after the procedure:

- urinalysis
- blood sampling at 8 hours, 16 hours and 24 hours after the procedure, for assessment of Total CK/CK MB
- 12-lead ECG
- connection to 24 hour Holtter monitor

Adverse events and concomitant medications will be monitored continuously during the procedure and recorded on the patient's CRF.

6.2.1.3 Daily during hospitalization

The patient must remain hospitalized for at least 48 hours after the procedure. The following assessments and procedures will be carried out during each day of hospitalization, including day of discharge:

- physical examination
- vital signs
- 12-lead ECG
- blood and urine sampling for laboratory safety parameters (biochemistry [excluding troponin I or T], hematology and urinalysis) on day of discharge and only if not done within the previous 48 hours
- NT-proBNP on day of discharge and only if not done within the previous 48 hours
- serious/adverse events
- concomitant medication

6.2.1.4 Telephone Contact, Day 8, ±1

Patients who have been discharged from the hospital will be contacted by phone 7 days after application of BL-1040. The patient should be asked the following questions:

1. How have you been feeling since your discharge? Have you had any chest pain or experienced any shortness of breath?
2. Did you call your doctor for any reason? If so, when, and for what reason? Did you go to the emergency room for any reason? If so, when and for what reason?
3. Are you taking any medications? If so, which ones?

The information collected from this phone call is to be recorded in the patient's CRF.

6.2.1.5 Day 30, Day 90 and Day 180 (End of Study)

The patient will return to the hospital for the following assessments and procedures on Day 30, Day 90 and Day 180. The visit on Day 180 will be considered the End of Study visit. If a patient is discontinued prior to Day 180 for any reason, the following assessments should be done at the time of discontinuation.

Assessments to be carried out include:

- physical examination:
- vital signs
- 12-lead ECG

- connection to 24-hour Holter monitor; to be returned on Day 31/Day 91/**Day 181**
- blood and urine sampling for laboratory safety parameters (biochemistry [excluding troponin I or T], hematology and urinalysis)
- NT-proBNP
- echocardiography
- MRI, if patient agrees
- completion of the Minnesota Living with Heart Failure® questionnaire
- serious/adverse events
- concomitant medication

6.2.1.6 Extended safety follow-up (Months 12, 24, 36, 48, 60 ±30 days)

Patients will return to the hospital yearly for completion of follow-up assessments.

Assessments are to include::

- physical examination
- vital signs
- 12-lead ECG
- connection to 24-hour Holter monitor; the patient is to be connected at the time of the follow-up visit, and the monitor is to be returned the following day
- blood and urine sampling for laboratory safety parameters (biochemistry [excluding troponin I or T], hematology and urinalysis)
- echocardiography
- completion of the Minnesota Living with Heart Failure® questionnaire
- completion of the following questions:
  - How have you been feeling since your last check up?
  - Have you been hospitalized for any reason? If so, when, and for what reason?
- serious/adverse events
- concomitant medication

6.3 Study evaluations and procedures

Safety will be evaluated by analyzing the results of physical examinations, laboratory examinations and cardiac assessments, as well as AEs (Section 7) and vital signs. Assessments will be carried out at the time points specified in Section 6.2, and as shown in Table 6.1.

All safety related investigations are to be performed by the Principal Investigator or a medically qualified designee, who is responsible for the overall treatment of the patient.

6.3.1 Safety

6.3.1.1 Physical examinations

Physical examinations will include height (Screening only), weight, and a general assessment of overall body systems (cardiovascular, respiratory).

6.3.1.2 Vital signs

The following vital signs will be assessed:

- pulse rate

- blood pressure (supine, systolic and diastolic)
- body temperature

The actual blood pressure and pulse rate should be recorded in the patient's CRF. Rounding of values is not allowed.

The following ranges will be used to define acceptable blood pressure:

- supine systolic blood pressure: 100 - 160 mmHg
- supine diastolic blood pressure: 60 - 95 mmHg
- supine pulse <100 bpm

Body temperature should be measured using the same methodology at each assessment, and should be measured in decimals.

6.3.1.3 ECGs

A standard supine 12-lead ECG shall be recorded. ECG morphology and ECG intervals (PR, RR, QRS, QT, and QTc) will be determined: QTc will be calculated using Bazett's formula.

Patients will be connected to a 24-hour ambulatory Holter monitor at each follow-up visit (Day 30, Day 90, Day 180).

Printouts/copies must be placed in the patient's chart, clearly labeled with the patient number, time, date, visit, and study number, and signed by the Investigator. A core laboratory will evaluate the results of both the ECG and Holter.

6.3.1.4 Echocardiograms

Echocardiograms will be performed and recorded according to specific criteria established for this study, and provided in a separate Echocardiogram Reference Manual. The same parameters will be measured at each assessment, throughout the study.

A core laboratory will evaluate echocardiograms.

The Principal Investigator, the Sponsor or the ISMB may review echocardiograms at any time if any safety concerns arise. Echocardiograms will be performed at the times indicated on the Schedule of Events and in Sec. 6.2 of the protocol.

6.3.1.5 MRIs

While the MRI is an optional procedure for cardiac assessment at Screening and all follow-up visits (Day 30, Day 90, Day 180/End of Study), patients should be encouraged to undergo the procedure at each relevant visit. Performance of the procedure is always contingent upon patient agreement.

MRIs will be performed according to specific criteria established for this study, and provided in a separate MRI Reference Manual. A core laboratory will evaluate MRIs.

The Principal Investigator, the Sponsor or the ISMB may review MRIs at any time if any safety concerns arise.

6.3.1.6 Clinical safety evaluations

Safety blood sampling

All laboratory samples will be processed at the local laboratory, except for NT-proBNP, which will be assessed at a core lab.

The Investigator must review the laboratory assessments (initialed and dated) within 24 hours after the receipt of those results. Out of range values will be interpreted by the Investigator with a comment of "not clinically significant" (NCS) or "clinically significant" (CS). Clinically significant abnormal laboratory values must be repeated on the appropriate clinical follow-up arranged by the Investigator and documented on the lab report until the lab value has stabilized or has returned to a clinically acceptable range (regardless of relationship to BL-1040). Any laboratory value that remains abnormal at the End of Study visit and is judged to be clinically significant will be followed according to accepted medical standards for up to 30 days or until resolution of the abnormality.

Approximately 15 mL safety blood samples will be collected at the time points indicated in Sec 6.2 and shown in Table 6.1. Analyses will include:

- biochemistry
  - total protein
  - albumin
  - total bilirubin
  - ALT
  - AST
  - GGT
  - LDH
  - alk phosphate
  - glucose
  - sodium
  - potassium
  - calcium
  - phosphate
  - urea/BUN
  - creatinine
  - PTT or ACT
  - troponin I or T (Screening only)

- hematology
  - red blood cell count
  - hemoglobin
  - hematocrit
  - mean cell hemoglobin
  - mean cell hemoglobin concentration
  - mean cell volume
  - white blood cell count and differential
  - platelet count

- cardiac biomarkers
  - Total CK/CK MB
  - NT-proBNP

- urinalysis

- urine protein
- urine glucose
- urine blood
- leukocytes
- nitrites
- urobilinogen
- bilirubin
- pH
- specific gravity
- ketones

If dipstick analysis reveals any pathological results, a full urine analysis will be conducted and the following should be checked:

1. Color
2. Appearance
3. Leukocytes + erythrocytes per HPF (High Power Field)
4. Squamos epithelial cells
5. Non squamos epithelial cells
6. Yeast in urine
7. Amorphous cells
8. Mucous in urine
9. Casts
10. Crystals

6.3.2 Core laboratories

Results of echocardiograms, ECGs, Holters, angiographies, and MRIs will be evaluated at Biomedical Systems:

Biomedical Systems
1945 Ch. de Wavre
B-1160 Brussels-Belgium
phone: +32 2 661 20 70
fax: +32 2 661 20 71
email: sjacobs@biomedsys.com

NT-proBNP samples will be assessed at the central laboratory at the University of Heidelberg:

Universitatsklinikum Heidelberg
Zentrallabor
Im Neuenheimer Feld 671
69120 Heidelberg, Germany
Tel.: 06221-56-8803
Fax: 06221-56-5205

6.4 Minnesota Living with Heart Failure® questionnaire

The Minnesota Living with Heart Failure® questionnaire (MLHQ) is a standardized and validated questionnaire designed to measure the effects of heart failure and treatments for heart failure on an individual's quality of life (ref. 6-8). The questionnaire measures the effects of symptoms, functional limitations, and psychological distress on the individual's life. These items are measured using a 6 point Likert scale (0-5) to indicate how much each of 21 items has affected their quality of life.

The scales will be administered by the Investigator or trained/designated personnel, in the local language.

7 Adverse and Serious Adverse Events

7.1 Adverse event definition

An adverse event (AE) is any untoward medical occurrence in a clinical trial patient who was administered a medicinal product and/or medical device and which does not necessarily have a causal relationship with this treatment. This includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory detected changes occurring in any phase of the clinical study whether associated with the study drug/device and whether or not considered related to study intervention. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or drug/device interaction. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation need not be considered AEs. Discrete episodes of chronic conditions occurring during a study period should be reported as AEs in order to assess changes in frequency or severity.

AEs should be documented in terms of signs and symptoms observed by the Investigator or reported by the patient at each study visit. A medical diagnosis should be added.

Pre-existing conditions or signs and/or symptoms (including any which are not recognized at study entry but are recognized during the study period) present in a patient prior to the start of the study should be recorded in the Medical History form within the patient's CRF.

7.2 Recording adverse events

All non-serious AEs (serious or non-serious) will be recorded from the time of implantation of BL-1040 on Day 1 until the end of the active study period (Day 180); all serious AEs will be recorded from the time of implantation of BL-1040 until the end of the long term follow-up (Month 60). AEs are to be recorded on the appropriate AE pages in the patient's CRF: if the AE is serious, the appropriate box on the AE page of the CRF should also be ticked. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made then each symptom should be listed individually. The nature, time of onset and cessation, and any treatment provided shall be recorded.

According to "Medical Devices: Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices — GHTF/SG2/N54R8: 2006, Study Group 2 Final Document'', typical adverse events for medical devices include but are not limited to:

- a malfunction or deterioration in the characteristics or performance
- an incorrect or out of specification test result
- an inaccuracy in the labeling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies. Omissions do not include the absence of information that should generally be known by the intended users.
- use error

All AEs (serious and non-serious) shall be reported as specified in this section of the Protocol and the expanded Medical Device Reporting Guidelines, which will be provided to all investigators prior to the start of the study.

7.3 Pre-device events

The Investigator will report any pre-device event directly observed or mentioned by the patient from the time of signing Informed Consent until the implantation of BL-1040 on Day 1. Pre-device events are reported in the CRF with at least the nature, the start date and the treatment (if applicable).

7.4 General adverse events

Information on any AE must be recorded when volunteered by the patient, observed by study personnel, or elicited by a non-leading question, such as "How are you feeling?".

7.4.1 Assessment of severity of general adverse events

General events should be assessed according to the following scale:

- mild — the event is easily tolerated and does not interfere with usual activity; disappears without residual effects
- moderate — the event interferes with daily activity, but the patient is still able to function
- severe — the event is incapacitating and the patient is unable to work or complete usual activity; considered as unacceptable by the Investigator

7.4.2 Assessment of causality of adverse events

Every effort should be made by the Investigator to explain each AE, both serious and non-serious, and assess its causal relationship, if any, to implantation of BL-1040.

The relationship of BL-1040 to the event will be determined by how well the event can be understood in terms of one or more of the following

related	there is suspicion of a relationship between BL-1040 and AE (without determining the extent of probability); there are no other more likely causes and administration of BL-1040 is suspected to have contributed to the AE
possible	AE occurs within a reasonable time after the implantation of BL-1040 but can also be reasonably explained by other factors (as mentioned below)
unrelated	there is no suspicion that there is a relationship between BL-1040 and AE, there are other more likely causes and implantation of BL-1040 is not suspected to have contributed to the AE

Non-serious and serious AEs will be evaluated as two distinct types of events given their different medical nature. The Investigator will examine all events assessed as "serious" (Sec. 7.5.1) in order to determine, as far as possible, ALL contributing factors applicable to each serious AE.

Other possible contributors include:

- underlying disease
- Other medication
- protocol required procedure
- other (specify)

7.4.3 Follow-up of adverse events and assessment of outcome

All AEs will be followed to resolution (patient's health has returned to baseline status or all variables have returned to normal); until an outcome has been reached; stabilization (Investigator does not expect any further improvement of worsening of the event); or the event is otherwise explained, regardless of whether the patient is still participating in the study. Where

Page appropriate, medical tests and examinations will be performed to document resolution of the event. All follow-up information will be recorded in the patient's CRF until Day 180.

7.5 Serious Adverse Events

7.5.1 Definition of Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence or effect that led to one of the following outcomes:

- death of a patient, user or other person
- serious injury of a patient, user or other person
  Serious injury (also known as serious deterioration in state of health) is either:
  - a life threatening illness or injury *
  - permanent impairment of a body function or permanent damage to a body structure†
  - a condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
    The term "permanent" means irreversible impairment or damage to a body structure or function, excluding minor impairment or damage
    Medical intervention is not in itself a serious injury. It is the reason that motivated the medical intervention that should be used to assess the reportability of an event.
  - in-patient hospitalization‡ or prolongation of existing hospitalization
  - an event that might lead to death or serious injury of a patient, user or other person if the event recurs (sometimes called a ''near incident'')

*Life threatening: An AE is life threatening if the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

†Disabling/incapacitating: An AE is incapacitating or disabling if the event results in a substantial disruption of the patient's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g. sprained ankle).

‡Hospitalization: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for treatment that would not have been appropriate in the physician's office or out-patient setting.

Hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalization for "social" reasons) that are not the result of an AE need not be considered as AEs and are therefore not SAEs. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

¶Routine Clinical Procedure: procedure which may take place during the study period and should not interfere with the implantation of BL-1040 or any of the ongoing protocol specific procedures. If anything untoward is reported during an elective procedure, that occurrence must be reported as an AE, either 'serious' or non-serious according to the usual criteria.

For medical devices, typical serious adverse events include but are not limited to:

- use error (e.g. untrained user, incorrect route of administration) related to medical devices, which did result in death or serious injury
- damage to tissue or tissue function following administration of study device

- impairment of an organ or organ function following administration of study device
- interaction with concomitant treatment (other devices or drugs) that might lead to death or serious injury
- interaction with materials (e.g. catheters, stent), substances or gases entering into contact with the device during normal use that might lead to death or serious injury
- non-biocompatibility leading to serious irritation/allergy that results in in-patient hospitalization or prolongation of existing hospitalization

7.5.2 Pre-defined SAEs

For the purposes of this study, the following events will be defined as serious:

- re-infarction
- stroke or transient ischemic attack (TIA)
- acute heart failure (decompensation)

The occurrence of any of these events after implantation of BL-1040 will be considered an SAE; they are to be reported and followed up as specified in Sections 7.5.3 and 7.5.4.

7.5.3 Reporting serious adverse events

All Serious Adverse Events (SAEs) must be reported immediately by the Investigator without filtration, whether considered to be associated with BL-1040 and whether or not considered related to BL-1040. The Investigator must report SAEs within one calendar day of becoming aware of the event by telephone, fax or e-mail to the Study Contact for Reporting Serious Adverse Events as indicated below. This initial notification should include minimal, but sufficient information to permit identification of the reporter, the patient, study device, any medications administered, AEs, causality assessment and date of onset. The Investigator should not wait for additional information to fully document the event before providing notification. An acknowledgement letter will confirm the first notification. The report is then to be followed by submission of a completed SAE Report Form provided by Venn Life Sciences AG as soon as possible but at latest within 3 calendar days of the initial telephone/fax or e-mail report detailing relevant aspects of the AEs in question. All actions taken by the Investigator and the outcome of the event must also be reported immediately. For documentation of the SAE, any actions taken, outcome and follow-up reports, the SAE Report Forms are to be used. Where applicable, hospital case records and autopsy reports should be obtained.

Investigators must report SAEs to the appropriate ethics committee if requested by the committee and/or according to local legal requirements.

Study Contact for Reporting Serious Adverse Events.

Venn Life Sciences AG, Elisabethenstrasse 23/3, CH-4051 Basel

Fax:	00800 201 11 011
e-mail:	SAE@vlsworldwide.com
Tel:	+41 61 201 11 83

24/24 hour and 7/7 day availability

7.5.4 Follow-up of serious adverse events

All SAEs must be collected and documented until the end of the long term follow-up (Month 60), and followed up until the event either resolved, subsided, stabilized, disappeared or is otherwise

explained or the study patient is lost to follow-up. All follow-up activities must be reported, if necessary on one or more consecutive SAE report forms, in a timely manner. All fields with additional or changed information must be completed and the report form should be forwarded to the Study Contact for Reporting Serious Adverse Events as soon as possible but latest within 7 calendar days after receipt of the new information. Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Reports relative to the subsequent course of an AE noted for any patient must be submitted to Venn Life Sciences AG.

7.6 Treatment of adverse events

Treatment of any AE is at the sole discretion of the Investigator and according to current available best treatment. The applied measures should be recorded in the CRF of the patient.

7.7 Pregnancy

The Sponsor must be notified immediately of any pregnancy that occurs during the study. The SAE report form should be used to report the pregnancy, even though the pregnancy is not considered an SAE. Women who become pregnant during the study will be followed up until birth of the child. The health status of the newborn will be reported in the patient's CRF.

8 Data Evaluation and Statistics

In all analyses where a change from baseline is performed, baseline is defined as the last available value before device implantation.

8.1 Endpoints

The **primary** endpoints are occurrence of all adverse events including but not limited to:

- all MIs
- cardiovascular hospitalization
- serious ventricular arrhythmias sustained
  - VT (symptomatic or sustained VT [duration longer than 30 seconds or 100 beats, or associated with hemodynamic collapse]
  - VF
  - symptomatic bradycardia, pauses of longer than 3.0 seconds, complete atrioventricular block, Mobitz II atrioventricular block
- symptomatic heart failure (NYHA criteria + physical examination OR hospitalization due to heart failure)
- renal failure
- stroke
- death

Secondary Endpoints include the parameters:

- change from baseline in LV dimensions (end-systolic volume index, end-diastolic volume index, left ventricular mass)
- change from baseline in regional (infarct related) and global wall motion score
- change from baseline in ejection fraction
- cardiac rupture
- NT-proBNP

8.2 Estimated sample size

No formal sample size calculation was performed. Twenty patients followed up to Day 180 were deemed necessary to meet the objectives of this Phase I study. Taking into account drop-outs after the device implantation, thirty patients will be enrolled.

8.3 Planned methods of analysis

All data recorded will be presented in data listings and summary tables, as appropriate. Missing values will not be replaced. No formal hypothesis testing will be performed.

8.3.1 Analysis population

All participants who received the BL-1040 myocardial implant will be included in the safety analysis. Any excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be finalized prior database lock.

8.3.2 Analysis of demographics

Continuous demographic variables (age, height, weight) will be summarized using mean, median, standard deviation, minimum, maximum, and number of available observations.

Qualitative demographic characteristics will be summarized by counts and percentages. Other patient characteristics (medical history, clinical findings, prior medications, inclusion/exclusion criteria) will only be listed.

8.3.3 Analysis of safety

AEs will be described in individual listings and frequency tables by system organ class and preferred terms (MedDRA version 10.0 or higher), regardless of relationship as well as for related AEs. The severity of AEs will also be tabulated.

Vital signs will be listed and changes from baseline and raw results will be summarized by means and standard deviations.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges. Raw laboratory results and changes from baseline will be summarized by means and standard deviations.

12 lead ECG findings will be presented by listings and frequency tables, as appropriate. Continuous ECG data will be summarized using standard descriptive statistics.

The change from baseline in cardiac parameter (LV dimensions, wall motion score, ejection fraction) as well as the NT-proBNP data will be summarized using standard descriptive statistics.

8.4 Interim analysis

An interim safety analysis will be performed after 5 patients have completed the Day 30 visit, on all data collected up to this timepoint.

8.5 Final and follow-up reporting

The final clinical study report will be prepared based on data from Day 180, or End of Study, from the final patient. Thereafter, an annual safety report will be prepared after each yearly safety follow-up visit (Months 12, 24, 36, 48, 60).

8.6 Quality assurance

All data collected in the CRF will be double entered into a validated computerized clinical data management system (Clintrial). Laboratory values from the local lab will be entered into the CRF. Analysis of the data will only be performed after all queries have been resolved using an appropriate software for analysis (SAS 8.1).

9 Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice, the Declaration of Helsinki 2000 (Appendix A), and the rules and regulations of the European Union and Israel.

9.1 Informed Consent

The nature, purpose and potential risk of the study as well as the action of the BL-1040 myocardial implant will be explained to all patients both verbally and in writing. They will be given adequate time to consider the study before signing the consent form. Their questions will be actively encouraged. They will be informed that they may withdraw from the study at any time. This information is documented in the protocol and participants in the study will sign a consent form confirming that they have read and understood it; no study activities will take place until the consent form has been signed. They will also be given a Patient Information Sheet and copy of the consent form.

9.2 Authorities

The procedures laid out by the local regulatory authorities must be followed and all documents must be submitted to all concerned authorities, and where needed, approved before a clinical study may commence.

9.3 Protocol Amendments

There will be no alteration to the protocol without the express written approval of the Sponsor.

The local authorities or ethics committees must approve all major protocol amendments prior to implementation.

No protocol amendments should be adopted without prior written approval from the ethics committee except in the following cases:

- in order to eliminate immediate hazard to the patients,
- changes involving only logistical or administrative aspects of the trial. Then notification to the relevant authorities should be submitted.

In these cases, the implemented deviation or change should be submitted as soon as possible to the relevant authorities for review and approval.

No protocol deviations are anticipated. However, should any protocol deviations occur, the Principal Investigator must report the matter to the Sponsor as soon as reasonably practical. Details of the deviation and, if possible, the reason for its occurrence must be included in the study report.

Major modifications will need further approval, and will be submitted to the local authorities or ethics committees, according to local regulations, in the form of an Amendment. Minor administrative changes require only that the Chairman of the Ethics Committee be informed in writing without delay.

9.4 Patient confidentiality

Individual patient data obtained as a result of this study is considered confidential. A patient identification number will identify any patient data collected throughout the study only.

Data generated as a result of this study are to be available for inspection on request by all authorized Sponsor personnel, Venn Life Sciences AG personnel, audit personnel and regulatory authorities. The Informed Consent must clearly reflect this access.

9.5 Insurance

The compensation of the patient in the event of study related injuries will comply with the applicable obligatory requirements. Details will be included in the informed Consent.

9.6 Duration of the study

The active study phase for each patient is 180 days. Enrolment is expected to begin in Q1 2008; the study is expected to end **Q1 2010.**

10 Data Handling and Record Keeping

10.1 Documentation

Records must be retained for 15 years after study completion

10.2 Case Report Forms

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be transferred into the study database. Case Report Forms (CRFs) should be completed by the Investigator or delegated personnel.

CRFs will be provided for each patient. All data will be entered in black ink. Data/corrections entered will be signed or initialed by the study personnel undertaking that procedure. Overwriting data or use of liquid correcting fluid is not allowed. Detailed instructions are provided with the CRF.

10.3 Monitoring and quality control

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of BioLine Innovations Jerusalem, Venn Life Sciences AG(CRO), auditing personnel and relevant local regulatory authorities.

Regular on-site visits for monitoring of study activities and data recording will be scheduled. Formal reports of these visits will be generated and copies provided to relevant Sponsor and study personnel.

10.4 Publication policy

The results of the study are the property of the Sponsor. All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, in advance of submission. Co-authorship with any Sponsor personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

11 References

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Appendix A: Declaration of Helsinki

Initiated: 1964 17.C Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles
for

Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and

therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in

the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

♣ ♣ ♣

Instructions for Use

1. Patients should respond to the questionnaire prior to other assessments and interactions that may bias responses. You may tell the patient that you would like to get his or her opinion before doing other medical assessments.

2 Ample, uninterrupted time should be provided for the patient to complete the questionnaire.

3. The following instructions should be given to the patient each time the questionnaire is completed.

   a. Read the introductory paragraph at the top of the questionnaire to the patient.

   b. Read the first question to the patient - "Did your heart failure prevent you from living as you wanted during the past month by causing swelling in your ankles or legs"? Tell the patient. "If you did not have any ankle or leg swelling during the past month you should circle the zero after this question to indicate that swelling was not a problem during the past month". Explain to the patient that if he or she did have swelling that was caused by a sprained ankle or some other cause that was definitely not related to heart failure he or she should also circle the zero. Tell the patient, "If you are not sure why you had the swelling or think it was related to your heart condition, then rate how much the swelling prevented you from doing things you wanted to do and from feeling the way you would like to feel". In other words, how bothersome was the swelling? Show the patient how to use the 1 to 5 scale to indicate how much the swelling affected his or her life during the past month - from very little to very much.

4. Let the patient read and respond to the other questions. The entire questionnaire may be read directly to the patient if one is careful not to influence responses by verbal or physical cues.

5. Check to make sure the patient has responded to each question and that there is only one answer clearly marked for each question. If a patient elects not to answer a specific question(s) indicate so on the questionnaire.

6. Score the questionnaire by summating the responses to all 21 questions. In addition, physical (items 2, 3, 4, 5, 6, 7, 12 and 13) and emotional (items 17, 18, 19, 20, and 21) dimensions of the questionnaire have been identified by factor analysis, and may be examined to further characterize the effect of heart failure on a patient's life.

LIVING WITH HEART FAILURE QUESTIONNAIRE

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. The items listed below describe different ways some people are affected. If you are sure an item does not apply to you or is not related to your heart failure then circle 0 (No) and go on to the next item. If an item does apply to you, then circle the number rating how much it prevented you from living as you wanted.

Did your heart failure prevent you from living as you wanted during the last month by:

		No	Very little				Very much
1.	Causing swelling in your ankles, legs. etc.?	0	1	2	3	4	5
2.	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3.	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4.	Making your working around the house or yard difficult?	0	1	2	3	4	5
5.	Making your going places away from home difficult?	0	1	2	3	4	5
6.	Making your sleeping well at night difficult?	0	1	2	3	4	5
7.	Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8.	Making your working to earn a living difficult?	0	1	2	3	4	5
9.	Making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10.	Making your sexual activities difficult?	0	1	2	3	4	5
11.	Making you eat less of the foods you like?	0	1	2	3	4	5
12.	Making you short of breath?	0	1	2	3	4	5
13.	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14.	Making you stay in a hospital?	0	1	2	3	4	5
15.	Costing you money for medical care?	0	1	2	3	4	5
16.	Giving you side effects from medications?	0	1	2	3	4	5
17.	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18.	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19.	Making you worry?	0	1	2	3	4	5
20.	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21.	Making you feel depressed'?	0	1	2	3	4	5

SCHEDULE 1.31

DESCRIPTIONS OF OTHER ON-GOING TRIALS

Name of Study	Estimated Duration	Estimated End Date
[**]	[**]	[**]
[**]	[**]	[**]
[**]	[**]	[**]

SCHEDULE 1.35

OUTLINE OF STRUCTURE FOR PIVOTAL CLINICAL TRIAL FOR PRIMARY INDICATION

(see Schedule 3.1)

SCHEDULE 1.42(a)

INDEPENDENT SAFETY MONITORING BOARD CHARTER

Independent Safety Monitoring Board

Charter

For

Bioline Innovations Jerusalem

Protocol No. BL-1040

A Phase I, multi-center, open label study designed to assess the safety and feasibility of the injectable BL-1040 implant to provide scaffolding to infarcted myocardial tissue

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1. PROTOCOL BL-1040

A Phase I, multi-center, open label study designed to assess the safety and feasibility of the injectable BL-1040 implant to provide scaffolding to infarcted myocardial tissue.

Venn Life Sciences AG has been contracted by Bioline Innovations Jerusalem to provide services as the Contract Research Organization (CRO) for the trial.

2. SCOPE OF THE ISMB CHARTER

The International Independent Safety Monitoring Board (ISMB) was formed to monitor the safety of patients participating in this trial on an ongoing basis.

The ISMB will evaluate quality, accuracy and timeliness of data flow and assure confidentiality of data.

The ISMB will develop stopping rules for the termination of the study prior to the initiation.

Bioline Innovations Jerusalem will forward the charter to Regulatory Authorities, and/or Ethics Committees as necessary.

The objective of the ISMB Charter is to outline the specific purposes and functions of the ISMB. In addition, it describes the procedures for data abstraction and data delivery conventions to and from the ISMB members for review purposes.

3. COMPOSITION OF THE ISMB

The ISMB is composed of three members, three voting members including the Chairman. In addition a bio-statistician will consult the ISMB however will not attend as a voting member. The members are independent physicians in the field of cardiology and a bio-statistician experienced in evaluating safety data from cardiology clinical studies. Prof. Lincoff will serve as Chairman of the ISMB. All ISMB members have been approved by the sponsor, Bioline Innovations Jerusalem.

By signing the ISMB Charter, voting ISMB members verify that they do not have a vested interest in the outcome of the study, nor do they have a financial conflict of interest. ISMB members are not employees of Bioline Innovations Jerusalem have outside employment and will not be involved in patient recruitment or as investigators in the study.

The ISMB members are expected to serve until the study is completed. Should a member resign, the reason and effective date of resignation must be submitted in writing to Bioline Innovations Jerusalem and the ISMB Chairman. A replacement member will be sought by Bioline Innovations Jerusalem in consultation with the ISMB Chairman.

Except for the initial meeting of the ISMB where the background data on BL-1040 and the study design will be discussed by Bioline Innovations Jerusalem's' representatives, Bioline Innovations Jerusalem will not participate in the ISMB meetings unless requested by the ISMB.

ISMB Administration

From Venn Life Sciences AG, the ISMB Coordinator will arrange for the provision of the data and narratives required by the ISMB. Bioline Innovations Jerusalem will provide administrative, logistical and coordinating services to the ISMB.

ISMB Contacts & Consultants

The Chairman will be the representative of the ISMB who will be responsible for timely official communications between the ISMB and Bioline Innovations Jerusalem. The Chairman will provide leadership and oversee that the direction of ISMB meeting operations are in accordance with the ISMB charter.

From the sponsor, Bioline Innovations Jerusalem, an identified representative will serve as the primary contact person for the ISMB. The sponsor primary contact is named on the ISMB charter. This individual is not considered to be a member of the ISMB and will only attend open and final sessions of ISMB Data Review Meetings.

From Venn Life Sciences AG, the ISMB Coordinator will serve as the primary contact person for any questions the ISMB members have regarding the contents of the ISMB Data Reports. This individual is not considered to be a member of the ISMB and will

only attend open and final sessions of ISMB Data Review Meetings. Additional individuals may also be invited to attend the open and final sessions of the ISMB Data Review meetings, as deemed appropriate.

The ISMB Chairman will ensure that ISMB contacts are ***not*** exposed to the ISMB review of the data until the ISMB has arrived at a conclusion. ISMB contacts may ***not*** be present during closed sessions, when the ISMB Data Report is reviewed, ISMB deliberations are made, ISMB recommendations are discussed and/or ISMB voting procedures are conducted.

4. ISMB ROLE & RESPONSIBILITIES

The ISMB is an independent expert advisory group commissioned and charged with the responsibility of evaluating accumulating data at regular intervals and ensuring the safety of the subjects enrolled in the study by monitoring cumulative safety data collected in the clinical program and providing recommendations to Bioline Innovations Jerusalem based on review of this data. The ISMB will contribute to efficient conduct of the trial by providing a fast review of emerging findings from the study. This ISMB will consist of physicians with expertise in cardiovascular disease, particularly in the area of coronary artery disease and with experience monitoring safety of drugs and/or devices for cardiovascular applications, and will have no participation in the trial in any other capacity.

These reviews in subsets of patients will have the objective of searching for signals of clinically important adverse safety findings that may be indicative of risk to currently enrolled patients as well as increased risk for future patients. In these reviews, the ISMB will assume a conservative approach in assessing safety.

The Chairman will be directly responsible for reporting the outcome of all ISMB meetings and be the primary contact for any emergency meetings, as appropriately convened. He will be a voting member of the ISMB. The Chairman will also be responsible for the preparation of the report and/or recommendations to Bioline Innovations Jerusalem.

The three voting members of the ISMB (along with the Chairman) will be responsible for evaluating the safety data and making recommendations on the continuation of the study as set out in the protocol. They may also make other pertinent safety recommendations for the conduct of the study. They will be guided by the ISMB Biostatistician's evaluation of the data, as required.

The bio-statistician will be involved in conducting any analysis that the ISMB recommends. The Bio-statistician will be responsible for designing and maintaining the safety database that the ISMB will use for its analysis. This database may differ from the database by Venn Life Sciences AG and, as such, is meant only for the use of the ISMB. The database will be created in such a way that it is reproducible and can be audited, if necessary. If the ISMB is considering a recommendation of premature termination of the study, the bio-statistician can contact Venn Life Sciences AG for additional data and/or for the performance of confirmatory analysis. The Bio-statistician can also arrange for the necessary ISMB communications to be documented and stored and only to be released after study completion.

The ISMB will ensure that this study meets the highest standards of patient safety. In their analysis of the data from the patients, the ISMB will be focused on determining if there is a signal of clinically significant pattern of change in safety parameters that may lead to termination of study. This may require the ISMB to perform/request additional data/analyses prior to making a decision.

The operating procedures of the ISMB are based on and are in compliance with guidance and definitions of the International Conference on Harmonization and the Food and Drug Administration. The ISMB will conduct all of its operations under the ICH Good Clinical Practices (GCP).

Specifically, the ISMB is authorized and charged to perform the following functions:

- review 30 day safety data patients from the first 2 sequentially enrolled patients to determine whether 3 additional patients may be enrolled; after reviewing the 30 day safety data from these 3 additional patients, will determine whether the rest of patients may be enrolled
- within 30 days of enrolment of each successive group of 5 patients receiving the device, will review all Serious and Severe Adverse Events occurring to date and will recommend continuation, discontinuation, or modification of the procedure or protocol, based on a determination of whether the occurrence of serious, unexpected, or device-related adverse events (Sec. 7 in protocol) might outweigh the potential benefit achievable with the device
- review emerging findings in patients and identify potential safety concerns with BL-1040
- will receive information, on an expedited basis, on all Serious and Severe Adverse Events, clinically significant laboratory values (as defined in the study safety plan), ECG abnormalities and vital signs that are associated with Serious and Severe Adverse Events, and data from patients who decided to withdraw from the study due to Serious and Severe Adverse Events. All Serious and Severe Adverse Events that occur in the catheter lab during the administration of BL-1040 or the hospitalization period after the procedure should be reviewed

promptly by the ISMB. The ISMB will review this information and may decide to interrupt, alter, or terminate the trial.

- will adjudicate whether or not an event is unexpected, based on a pre-specified list of expected Serious and Severe Adverse Events as well as clinical judgment within the study population.

All ISMB members will review the safety data provided by the CRO. The members will reach their own individual decision on the relatedness and the potential hazard posed by the event. The ISMB will then collectively discuss the cases. In the event the majority opinion of the Board is that the events do not pose any significant risk then the ISMB will recommend continuing the trial as designed. However, if the Board decides that undue risk could accrue from continuation of the study as designed, the ISMB has the freedom to recommend appropriate changes to the study selection criteria, safety evaluations, etc. In addition, the CRO will provide datasets and listings capturing disposition, AEs, clinically significant Echocardiography, MRI, angiography, Holter, ECG vital signs/laboratory changes, once all patients complete study.

5. VENN LIFE SCIENCES AG ROLE & RESPONSIBILITIES

Venn Life Sciences AG will provide coordinating services for the study. The ISMB Coordinator will provide information, on an expedited basis, on all Serious and Severe Adverse Events, clinically significant laboratory values (as defined in the study safety plan, ECG abnormalities and vital signs that are associated with Serious and Severe Adverse Events as required, to the ISMB members. Venn Life Sciences AG will be charged with the following responsibilities:

- To identify a specific individual to interface with the ISMB.
- To provide all required information in advance of the meeting in a mutually agreeable format approved at the initial meeting of the ISMB.
- To provide a standard safety narrative for all patients who withdraw from the study due to Serious or Severe Adverse Events.
- To provide specific meeting issues in advance of the meeting.
- To keep the ISMB Chairman informed of any serious safety issues as the study progresses
- To inform each principal investigator of the ISMB recommendations, as required.
- To notify Bioline Innovations Jerusalem of any issues related to the ISMB which might negatively influence the study.

6. BIOLINE INNOVATIONS JERUSALEM'S RESPONSIBILITIES

Bioline Innovations Jerusalem will be responsible for the following:

- To make any necessary changes to the protocol recommended by the ISMB and approved by Bioline Innovations Jerusalem.
- To ensure that the ISMB is operating as needed for the purpose of the study.

7. ONGOING COMMUNICATIONS & NOTIFICATIONS

The ISMB Chairman will receive relevant information regarding serious adverse events and Early Terminations on an ongoing basis. The ISMB Chairman will determine whether further distribution of this material to the remaining voting ISMB members is necessary.

8. DATA REVIEW MEETINGS

ISMB Data Review meetings will be held in person or through teleconferences based on the volume of data to be reviewed. The ISMB Coordinator will establish the agenda for each ISMB Data Review meeting, with input from Bioline Innovations Jerusalem and the ISMB Chairman.

It is expected that there will be one initiation and at least three scheduled ISMB Data Review meetings. The initiation meeting will be held via face-to-face format, while the Data Review Meetings may be held via teleconference.

The first 2 patients will be sequentially enrolled into the study. After the 1st patient has completed Day 30 assessments, the Independent Safety Monitoring Board (ISMB, Sec. 4.3) will review the patient's data through Day 30 (first ISMB meeting). The ISMB will then decide whether to give approval to enroll the 2nd patient. After the 2nd patient has completed Day 30 assessments, the ISMB will again review the data and provide approval for enrollment of the next 3 patients (2nd ISMB meeting). After all 3 patients have completed Day 30 assessments, the ISMB will review the data from these patients and provide approval for opening enrollment to the rest of the patients (3rd meeting)

The ISMB may also elect to hold ad hoc meetings outside of the scheduled dates, if deemed necessary. For instance, as the ISMB Chairman will receive information regarding reported serious adverse events on a regular basis, ad-hoc ISMB meetings may also be held on a triggered basis (e.g. in response to a high number of safety events).

Voting

Input must be obtained from all three ISMB members, for voting purposes. The ISMB will strive for a consensus opinion regarding the data reviewed. If ISMB consensus is not possible, a majority vote will be required, to determine the final ISMB recommendation. If the ISMB vote does not result in a clear majority, the ISMB Chairman will assemble and present majority and dissenting opinions for all recommendations considered.

Meeting Minutes

ISMB Data Review meeting minutes will be divided by session and will reflect the attendance of voting ISMB members, the ISMB Coordinator, ISMB contacts and consultants and other individuals, as well as whether each individual attended in person or via teleconference.

Since all details of ISMB deliberations must be kept strictly confidential among members of the ISMB, portions of the ISMB Data Review meeting minutes must remain confidential until the completion of the final study analysis.

The ISMB Chairman will file all minutes from all sessions, centrally. Once the final study analysis is complete, the ISMB Chairman will forward the central file of all ISMB minutes for all sessions to Bioline Innovations Jerusalem for appropriate filing.

9. RECORDS RETENTION

The ISMB Chairman should maintain a record of all ISMB minutes until the investigation of the study device is discontinued. After this period, the ISMB Chairman will forward to the sponsor all records to the sponsor to determine if further retention and/or archiving is necessary.

Data Source and Content

10. ISMB COMMUNICATION OF FINAL CONCLUSIONS

The ISMB Chairman will contact Bioline Innovations Jerusalem within two working days after an ISMB meeting (via facsimile or telephone) to notify them of recommendations forthcoming from that meeting. Bioline Innovations Jerusalem will act upon these recommendations as appropriate, i.e., the final decision will rest with Bioline Innovations Jerusalem. Bioline Innovations Jerusalem's VP of Medical Affairs or designee will notify the project team and the CRO of the ISMB recommendations.

Bioline Innovations Jerusalem's VP of Medical Affairs will also write a memo to the files documenting the recommendations of the ISMB and convey to all investigators the decision to continue/discontinue the study.

11. IMPLEMENTATION OF THE ISMB RECOMMENDATIONS

The decision to implement the recommendations of the ISMB will be made by Bioline Innovations Jerusalem. Bioline Innovations Jerusalem will notify the ISMB of the actual action taken, in response to all recommendations.

If the ISMB recommends early study termination or protocol modification and such action is not accepted or implemented, Bioline Innovations Jerusalem will address this decision with the ISMB in writing.

12. CONFIDENTIALITY

The ISMB will maintain a strictly confidential relationship to the study data. The ISMB will only reveal specific details and information associated with ISMB data review to appropriate parties, as specified by this ISMB Charter.

SCHEDULE 2.3

EXISTING PRODUCT AGREEMENTS

[**]

SCHEDULE 3.1

INITIAL DEVELOPMENT PLAN

Project Boston Clinical Development Plan

Objective

This product is a unique concept, and will require a unique and sophisticated development plan to satisfy all stakeholders.

This product has been given a regulatory designation as a device (rather than drug). The objective of this development plan is to leverage that designation for a rapid and efficient regulatory approval, while providing adequate evidence for safety within the intended patient population.

Strategy

The strategy is to complete a minimal additional amount of preclinical safety in parallel with the clinical development program. [**].

The filing will be based on a [**]. We note that the current phase 2 study has no control group, and can give only general information about safety and tolerability, and no real information on efficacy in humans. For this reason the [**] will be designed with a 'vanguard' cohort of approximately [**] patients. Once the vanguard has completed 6 months of follow up, and interim analysis will be performed, assessing the study for 1) safety, 2) efficacy or futility and 3) performance of the endpoint. Specific, detailed and comprehensive criteria will be established to allow for stopping or continuation, or adjustments in sample size or inclusion criteria. The rules for the interim analysis will be agreed with regulatory authorities in advance of any unblinding, and appropriate adjustments will be made for type 1 error.

Following the interim analysis the number of participating centers will be increased to speed enrollment, and the study will continue to completion.

Endpoint and sample size

We will define [**] and then power the study to show at least a [**] with BL-1040 compared to placebo. This difference is clinically meaningful.

To give maximum power we want to define an endpoint that has a [**] after treatment, which would be reduced to [**]. We will design a [**] that ensures an event rate that is [**] in the control arm.

Failure could include [**] Any one of these events and the patient is [**]; none of these events and the patient is considered [**]. It is possible that other clinically relevant events may be added to the composite.

Next we will estimate how often each of these events will happen. [**].

Control Group Event Rate	Treatment Group Event Rate	Sample size per arm 90% power and type 1 error < 5%	Total
[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]

Although not required under device approval regulations, approximately [**] patients would be desirable for a safety database. If we assume that the placebo event rate will be approximately [**], we would estimate the sample size of the pivotal study to be approximately [**] patients, including the [**] patients in the vanguard cohort.

Budget

	2009	2010	2011	2012	2013	2014	2015	2016	TOTAL
[**]	[**]	[**]	[**]	[**]	[**]	[**]			
[**]						[**]			
[**]							[**]		
[**]							[**]	[**]	
[**]								[**]	
TOTAL	[**]	[**]	[**]	[**]	[**]	[**]	[**]	[**]	[**]

Phase III Study

Budget will assume [**] of [**] patients, with a primary endpoint at [**] major adverse cardiac outcomes at [**], and a safety follow up annually for [**].

Clinical:		
Monitoring:		[**]
Per Patient total:	[**]	[**]
Pre Clinical	[**]	[**]
Total		[**]

Given that 15-20% of the total clinical costs are committed before the first patient is enrolled, we estimate that cost to decision point is approximately [**]. It may be possible to reduce cost to the

decision point by [**], trading off for time-to-launch. This alternative scenario has not been modeled.

Cost by Year ($M)

[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]

[**] **Study**

Budget will assume a [**] (including ethnicity) of [**] patients. Study will start in [**] and end [**]

Cost by Year ($M)

[**]	[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]	[**]

Timeline

Phase III Study

Enrollment w/ [**] per site per month	**Part 1**	**Part 2**
Total Enrollment	[**]	[**]
Active Sites	[**]	[**]
Enrollment/Site/Month (on average)	[**]	[**]
Monthly Study Enrollment	[**]	[**]
Time to Enroll Patient per Part (months)	[**]	[**]
TOTAL ENROLLMENT TIME (months)	[**]	

Trial Task	**End Date**
Initiate Project	[**]
FPI	[**]
[**]	[**]
LPI	[**]
DB Lock	[**]
CSR	[**]
Submit PMA	[**]

Probability of success

Based on the available preclinical data it is not possible to come to a firm estimate of POS at this time. However, there is evidence of efficacy in preclinical models, and a consensus among experts that the mechanism is plausible. Given the existing data on the prior use of this class of compounds in humans, the likelihood of adequate safety and tolerability seems higher than would otherwise be possible at this stage, and given the device designation, the probability of clinical and regulatory success is likewise higher than it might otherwise be. Assuming the likelihood of adequate safety at [**] and the likelihood of adequate efficacy at [**], the overall POS to filing is in the range of [**].

SCHEDULE 3.7

PRELIMINARY COMMERCIALIZATION PLAN

Preface:

This document is prepared for the management of BioLineRx as a basis for discussion only, and is intended to be indicative of Ikaria's current intent with respect to global commercialization of BL-1040. Actual launch plans will continue to evolve over time, in accordance with the evolution of market dynamics, the global environment for cardiovascular drugs and devices, and the emerging product profile of BL-1040.

I. Situation Analysis

a. Unmet Medical Need

Each year cardiovascular disease (CVD) causes over 4.3 million deaths in Europe. CVD is estimated to cost the European Union (EU) economy €192 billion a year. The main forms of CVD are coronary heart disease (CHD) and stroke. Just under half of all deaths from CVD are from CHD. CV is also a large problem in Japan, and is emerging as a public health issue even in the developing countries.

Each year smoking kills over 1.2 million people in Europe (450,000 from CVD)). Dietary patterns across Europe are playing an increasing role in CVD. Levels of physical inactivity are high in many European countries and levels of obesity are increasing across Europe in both adults and children. Over 48 million adults in Europe have diabetes and the prevalence is increasing.

Estimates for population and cardiovascular statistics are presented in Table 1

Table 1

Country	Population (000,000)	Est. Annual non-fatal MI (000)	Interventional Cardiologist	Annual PCI Procedures
[**]	10.4	34.7	230	28
[**]	5.5	18.3	85	15
[**]	5.3	17.7	80	14
[**]	64.4	214.7	1,772	172
[**]	82.3	274.3	1,500	219
[**]	16.7	55.7	266	45
[**]	0.3	1.0	14	1
[**]	58.1	193.7	1,879	155
[**]	40.5	135.0	730	108
[**]	7.6	25.3	124	20
[**]	61.1	203.7	1,000	163
Total Europe	**352.2**	**1,174.0**	**7,682**	**939**
[**]	127.0	423.3	2,500	339
[**]	21	70	373	56
Grand Total	**479.2**	**1,597.3**	**10,182**	**1,278**

b. Product

BL-1040, a novel, injectable, biodegradable polymer designed to be used in conjunction with Percutaneous coronary intervention (PCI) to provide mechanical scaffolding and reduce the risk of structural remodeling and heart failure in post-myocardial infarction (post-MI) patients, is currently in development and could be on the market as early as [**]. If successful, BL-1040 could be a breakthrough in the management of patients with cardiovascular disease and could represent a large commercial opportunity for Ikaria and **BioLineRx**.

c. Assessment of current level of CV practice

There is significant variability around the medical management of CHD across Europe. Theses groupings give a high level overview of the most common interventions:

Hospital admissions

Rates of admission for CVD vary considerably across Europe. In general, higher admission rates are found in Eastern European and Scandinavian countries. Similar geographical trends are seen for CHD.

Coronary revascularization and other procedures for CVD

While rates of revascularization vary widely across Europe, all countries have seen rates increase significantly since the 1990s. For example, since 1990 rates of PCI have increased fifteen-fold in Italy and twelve-fold in Finland. We expect that advances in medical technique and continued development of medical infrastructure around the world will drive continued growth in the coronary revascularization market.

Drugs

The use of drugs for secondary prevention in CHD patients varies considerably across populations, except in the case of anti-platelet drugs. Over 80% of patients took this form of drug (mostly aspirin). The use of beta blockers, lipid-lowering drugs and ACE inhibitors varies throughout the EU.

d. Pricing and reimbursement environment

The global market for cardiovascular drugs and devices is highly variable in terms of pricing and reimbursement climates.

Pricing

Pricing in the developed markets of western Europe tends to be similar to U.S. pricing, although prices can vary significantly by market, with Northern European markets having higher prices than southern European markets. By contrast, pricing in less developed markets (Eastern Europe, Latin America and the Far East) is highly variable, and will require careful study to ensure an appropriate price is selected in order to maximize penetration and profitability. A clear target product profile will be critical to assessment of pricing strategy in all markets.

Reference pricing is common practice in Europe, so timing of local launches must be carefully coordinated to ensure optimized pricing across the territory.

[**]

Reimbursement

With the exception of regulatory approval, reimbursement will be the single most important driver of commercial success.

The process by which products gain reimbursement can vary greatly from country to country, and may take a considerable amount of time. A recent study by IMS suggested that it was common for newly approved drugs to take between one and three years to gain widespread reimbursement coverage in the top 16 EU markets. Because most European countries operate centralized, government-financed health systems, it is not typical for patients to pay for treatments privately. In many countries where there is virtually no habit of citizens paying for their own healthcare, initiating selling activity without reimbursement would be virtually impossible, while inhabitants of some other countries may have no problem paying for healthcare out of their own disposable income.

Expected timing of reimbursement will, therefore, be a major driver of the timetable for building out sales infrastructure, and commencing selling activities. Ikaria will conduct extensive research between deal closing and launch to ensure that reimbursement conditions are clearly understood and that plans are in place to ensure broad and favorable access to major commercial markets.

II. **Commercialization Plan**

Product Positioning Strategy

Given the current expectations of the product profile, we aspire to — and expect that — BL-1040 will be positioned as the de facto standard for prevention of post-MI remodeling.

While this depends on the specific results of the clinical trials, the market conditions, including competitive scenario, and prevailing clinical practice standards, the goal will be to make BL-1040 use prevalent across a range of patient sub-groups that are at risk for remodeling. Specifically, the following patient groups will be addressed in the marketing plan:

- High-risk STEMI (includes patients with large myocardial Infarctions (MIs), anterior wall MIs and long lead time to PCI): [**]
- Other STEMI (includes all STEMI patients not considered of the highest risk): [**]
- NSTEMI (all patients who have an NSTEMI): [**]

In addition to the market development efforts listed above, the focus of marketing strategy will be on creating broad awareness of the significant long-term effects of remodeling as well as discussing the risks of myocardial damage and resulting negative consequences for all patients with MIs. In Europe, this will also require resetting of the current paradigm of treating non-primary PCI patients with medical therapy alone, and illustrating the benefits of treatment with a mechanical scaffolding device such as BL-1040.

Organization Size and Structure

As an experienced critical care company, Ikaria is committed to providing doctors and other medical professionals with a high level of customer service. Operating in a highly specialized, life-or-death environment Ikaria strives to match our customers own urgency and commitment to patient care.

To be successful in the area of post-MI care we anticipate creating an organization capable of delivering both the commercial and medical support desired by our target customer base. Ikaria intends to establish itself as the leader in critical care globally, and will use BL-1040 as the platform on which to establish its international presence. As such, we intend to build a robust but flexible organization with all the competencies necessary to achieve leadership of the field. Although BL-1040 will likely be Ikaria's first global product, we anticipate that our own internal pipeline candidates IK-1001 and Covox will not be far behind. The infrastructure envisioned by Ikaria and described in this document will therefore be sufficient to successfully commercialize all of Ikaria's present and future pipeline compounds.

Ikaria proposed to use a "hub and spoke" approach to commercializing BL-1040 in Europe—the "hub" being a European headquarters and the "spokes" representing local operating companies (LOCs) in major markets. The headquarters will provide overall strategic leadership and will spearhead European product development and commercial strategy, while local operating companies will be responsible for selling activity and local tactic implementation.

In addition to strategic marketing and leadership support, the European headquarters will be responsible for financial management and reporting of regional results, management of European regulatory affairs functions, development of a European clinical development program, development of effective key opinion leadership, development of compelling health economic data and development of HR strategies to maintain a strong and vibrant European organization.

The primary role of LOCs is to provide the necessary local sales and marketing efforts necessary to achieve financial objectives for BL-1040. In addition to the necessary commercial infrastructure, the local operating companies would also be staffed with the support functions essential to commercial success. This would include a small local finance team, medical affairs, regulatory affairs and human resource functions. The role of the local support staff is to implement strategic initiatives conceived at headquarters level, and support local initiatives as necessary. The medical affairs staff will be particularly important in supporting marketing in disseminating the full medical information on BL-1040 and the clinical specialists will also lead the training of physicians in using this product appropriately.

The LOC staffing level will be determined as a function of country population, disease prevalence and target doctor population. Sales Representatives will be recruited from companies with a depth of experience in cardiovascular drug and device sales to ensure we gain rapid access to the necessary prescriber base. Representatives will be compensated through a blend of base salary and sales incentive bonus, according to Ikaria's existing sales force incentive plan. (See Table 2)

Table 2

Country	Population (000,000)	Est. Annual non-fatal MI (000)	Interventional Cardiologist	Annual PCI Procedures (000)	Sales Reps
[**]	10.4	34.7	230	28	[**]
[**]	5.5	18.3	85	15	[**]
[**]	5.3	17.7	80	14	[**]
[**]	64.4	214.7	1,772	172	[**]
[**]	82.3	274.3	1,500	219	[**]
[**]	16.7	55.7	266	45	[**]
[**]	0.3	1.0	14	1	[**]
[**]	58.1	193.7	1,879	155	[**]
[**]	40.5	135.0	730	108	[**]
[**]	7.6	25.3	124	20	[**]
[**]	61.1	203.7	1,000	163	[**]
Total Europe	**352.2**	**1,174.0**	**7,682**	**939**	[**]
[**]	127.0	423.3	2,500	339	[**]
[**]	21.0	70.0	373	56	[**]
Grand Total	**479.2**	**1,597.3**	**10,182**	**1,278**	[**]

NB: The number of sales reps anticipated to be needed in each market has been estimated as a function of [**]

Launch Timelines

To maximize the value of BL-1040 Ikaria intends to be ready to launch at the earliest possible opportunity. As described above, a key driver of launch readiness in any given market will be the ability to access reimbursement for BL-1040. Without appropriate reimbursement in place, attempting to launch BL-1040 would be at best un-productive, and at worst, damaging to the long-term perception of the product.

Ikaria proposes to immediately undertake a battery of research and analysis to understand the market-specific reimbursement environments across major target markets. Results of this research would guide future launch plans, and help inform the timing of key investments in people and infrastructure.

Development of Ikaria's ex-US presence will occur differently throughout the world:

1) Ikaria already has management structures in place in Canada, Japan and Australia. These budding organizations would be expanded in the near term to allow essential market preparation activities to begin as soon as possible. As the product profile of BL-1040 becomes clearer, and the expectations for launch timing crystallize, this existing in-country leadership infrastructure will be expanded to include all the local sales and medical affairs capability necessary to a successful launch.

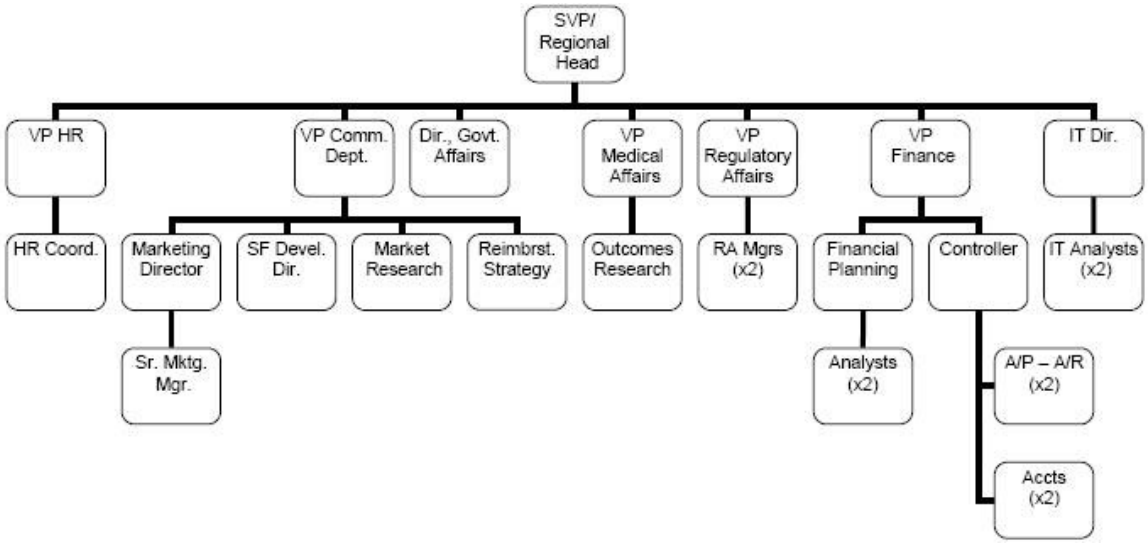
2) Establishment of a European Headquarters function would be a high priority. We anticipate filling key leadership positions as early as [**], so that high-level reimbursement, medical affairs and commercial strategic planning can commence. As a clearer view of the likely launch timeline for BL-1040 emerges, remaining HQ infrastructure will be built out to ensure a fully operational European headquarters well in advance of launch. In the event that a positive result emerges from the interim analysis and a decision is made to move up the commercial launch of the product, the development of the launch plans — including execution of reimbursement strategy and creation of marketing materials — will occur in parallel to the ramp up of the LOCs.

3) Additional, 2nd-tier markets will be evaluated in parallel with [**] commercial infrastructure development. Ikaria believes that there will be great potential for BL-1040 in markets such as [**], but will need more time to evaluate the optimal way to maximize sales in those territories.

[**]

Proposed European Structure

Headquarters



Human Resources

Human Resources will oversee European benefits programs, ensure compliance with local employment law, promote employee development and succession planning, and all functions necessary to building a world-class critical care business in Europe. The European HQ team will work closely with LOC country managers to ensure local employee needs are met and compliance with local laws is maintained. Local in-country contractors may be employed to deliver HR services at the local level.

Anticipated headcount: 2

Government Affairs

Appropriate reimbursement will be critical to the success of BL-1040. As described above, reimbursement can be highly variable across Europe. Development of a skilled government affairs capability within Ikaria Europe will be critical to our success, for BL-1040 as well as future Ikaria pipeline products.

Anticipated headcount: 1

Commercial Development

The European Commercial Development team is responsible for commercial strategy formulation across the European area, including both product and sales force strategy. The HQ marketing team will work closely with the Clinton, NJ-based marketing team to develop a cohesive global strategy suitable for implementation in European markets. The European team will have responsibility to ensure that brand strategies are implemented consistently across the area, and will perform market research to monitor performance and adjust strategy as appropriate. The team will also work in concert with country GMs and local marketing management to implement large-scale promotional and educations programs.

The European HQ team will also develop and implement European sales force strategies including development and maintenance of a customer relationship management system, sales skills training programs, and sales leadership development. The HQ team will work closely with LOC commercial management to ensure a top-class sales effort in each country.

Anticipated headcount: 5

Medical Affairs

Development of a strong base of key opinion leaders will be critical to the success of BL-1040. Cardiology is a fast moving, highly technical field, and for Ikaria to be a credible player we will need to make a significant commitment to supporting the medical community through education, research support, etc.

The European Medical Affairs team will take the lead in formulating strategy for the engagement of key opinion leaders in the formulation of brand development strategy, the development of brand champions and building high-level relationships between Ikaria and the medical community. The HQ Medical Affairs team will work closely with LOC Medical Affairs teams to align strategy across Europe and ensure a consistent medical approach.

The HQ Medical Affairs team will also be responsible for development of health outcome data to support cost-effectiveness arguments. The HQ team will work closely with LOC commercial teams to package health outcome data for effective presentation to in-country prescribers and reimbursement decision makers.

The HQ Medical Affairs team will also take responsibility for developing responses to requests for medical information about Ikaria products. The team will work with LOC Commercial and Medical Affairs teams to ensure a high level of customer support and satisfaction.

Anticipated headcount: 3

Regulatory Affairs

The European Regulatory Affairs (RA) team will lead all regulatory efforts on behalf of Ikaria's European operations. The HQ RA team will work closely with the Medical Affairs team to ensure development programs have maximal likelihood of success and that regulatory compliance is maintained at all times. The RA team will work in concert with in-country RA teams to execute on regulatory strategies and maintain product registrations with local authorities.

Anticipated headcount: 2

Finance

The European Finance team will support all local operating companies with financial reporting and planning functions as well as accounts payable and accounts receivable activities. The HQ team will consolidate European results and maintain a full European operating P&L. The HQ team will perform most of the finance functions on behalf of the European Area, with LOCs having minimal local requirement for finance headcount.

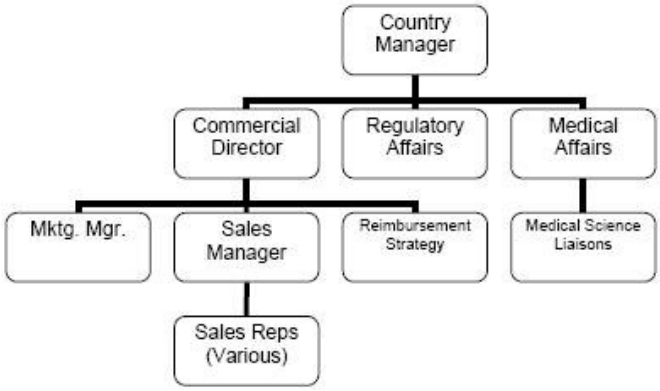
Anticipated headcount: 9

Information Technology

Ikaria's European IT requirements will be delivered by the European HQ team, with local support from 3rd-party contract services. The HQ team will liaise with Ikaria's corporate headquarters IT function in Clinton, NJ to ensure reliable systems functionality and robust customer support.

Anticipated headcount: 3

Local Operating Country (LOC) Structure



Human Resources

Human Resources support will be provided from HQ as described above. Specific local needs will be coordinated with HQ HR and delivered by local 3rd party providers

Anticipated headcount: None

Commercial Development

The LOC Commercial Development team is responsible for implementation of commercial strategy at the local level. The marketing team is responsible for implementation of European product strategy and for directing local tactical marketing in support of BL-1040. The LOC commercial director is also responsible for the development of a skilled critical care sales organization, including recruitment, training and management of reps and managers.

The number of sales reps required to promote BL-1040 will vary from country to country according to the market opportunity, the number of prescribing doctors, and the incidence of PCI procedures. (See Appendix A)

Anticipated headcount: Various

Medical Affairs

Maintenance of a strong relationships and robust medical affairs response capability will be essential for success at the local level. The LOC medical director will take responsibility for development of strong local relationships, coordination of company response to medical information requests. Clinical Specialists in each LOC will be responsible for training of physicians on use of product and for customer service.

Anticipated headcount: 1-2

Regulatory Affairs (RA)

The LOC RA team will work together with HQ RA teams to execute on regulatory strategies and maintain product registrations with local authorities.

Anticipated headcount: 1-2

Finance

The HQ team will perform most of the finance functions on behalf of the European Area, with LOCs having minimal local requirement for finance headcount.

Anticipated headcount: None

Information Technology

Ikaria's European IT requirements will be delivered by the European HQ team, with local support from 3rd-party contract services.

Anticipated headcount: None

SCHEDULE 4.3(a)

BIOLINERX WIRE TRANSFER INFORMATION

Bank Name:	[**]
Bank Address:	[**]
SWIFT Number:	[**]
IBAN Number:	[**]
Account Number:	[**]
Account Name:	[**]

EXHIBIT A

TECHNOLOGY EXCHANGE PLAN

Upon Ikaria's request, the following will be provided by BioLineRx to Ikaria or its designee:

7. All materials (original or copies as appropriate) in BioLineRx's possession and Control relating to Product, including documentation relating to Development and all regulatory filings, clinical information, and data and other documents relating to the On-Going Phase I/II Trial and the Other On-Going Trials.

8. Copies of all documents and available information in BioLineRx's possession and Control necessary for Manufacturing of Product at the time of technology exchange. These documents will include information necessary to assist Ikaria or its designee in setting up Manufacturing operations for such things as:

- raw material test methods, specifications, qualification and justification for use
- raw material vendor lists with part numbers
- analytical methods stated purpose, development, qualification and validation reports
- process development reports, laboratory notebooks and associated electronically stored data
- Manufacturing summary including
    - detailed process description with process schematics, operating parameters and target ranges, flow charts outlining critical process controls and steps, cartoons, verbal description including abbreviations, process scale, yield, and standard process instructions
    - in-process controls/tests and acceptance criteria including stated purpose of in-process tests
    - master batch record(s)
    - filling/packaging process
    - aseptic and process development and validation documents
    - facility and equipment requirements and design documents
    - descriptions of process equipment, including suppliers, part numbers, and historic invoices
    - product test methods, specifications and justification of specifications
    - product stability, test methods and qualification/validation reports, stability reports, shelf life recommendations

As available and agreed upon by the JDC at the time of a technology exchange, BioLineRx will provide requested technical manufacturing or engineering advice to Ikaria or its designee. Ikaria will ensure designee has necessary expertise in place to exchange the documentation and expertise in an orderly fashion.

EXHIBIT B

BIOLINERX PATENT RIGHTS

Family 1

INJECTABLE CROSS-LINKED POLYMER PREPARATIONS AND USES THEREOF

Country	Earliest Priority	Entry Date	Filing Date Application No.	Issue Date Patent No.	Status	Owner
[**]	[**]		[**]		[**]	[**]
[**]	[**]	[**]	[**]		[**]	[**]
[**]	[**]	[**]	[**]		[**]	[**]
[**]	[**]	[**]	[**]		[**]	[**]
[**]	[**]	[**]	[**]		[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]	[**]	[**]	[**]
[**]	[**]	[**]	[**]		[**]	[**]
[**]	[**]	[**]	[**]		[**]	[**]
[**]	[**]		[**]	[**]	[**]	[**]

Family 2

A METHOD OF TREATING MUSCLE TISSUES

Country	Earliest Priority	Entry Date	Filing Date Application No.	Issue Date Patent No.	Status	Owner
[**]	[**]		[**]	[**]	[**]	[**]

PAYMENT DATE EXTENSION AMENDMENT

Ikaria Development Subsidiary One LLC, a Delaware limited liability company having a principal place of business at 6 State Route 173, Clinton, NJ 08809, USA ("Ikaria"), BioLineRx Ltd., a corporation organized and existing under the laws of the State of Israel and having a principal place of business at 19 Hartum Street, P.O. Box 45158, Jerusalem 91450, Israel ("BioLineRx Ltd."), and BioLine Innovations Jerusalem L.P., a limited partnership organized and existing under the laws of the State of Israel and having a principal place of business at 19 Hartum Street, P.O. Box 45158, Jerusalem 91450, Israel ("BioLine Innovations"; together with BioLineRx Ltd., "BioLineRx") are party to an Amended and Restated License and Commercialization Agreement dated as of the 26th day of August, 2009 (the "Agreement"). Any defined terms used herein shall have them meaning ascribed thereto in the Agreement.

Pursuant to Section 4.1(a) the Agreement, Ikaria is required to make a milestone payment to BioLineRx of USD $10,000,000 upon the Successful Completion of the On-Going Phase I/II Trial (the "Second Milestone Payment") on or before [**]. BioLine and Ikaria are currently in discussions to determine whether Ikaria is required to withhold United States federal income taxes from the Second Milestone Payment. In order to enable the parties to complete those discussions, Ikaria and BioLine hereby agree that the due date for the Second Milestone Payment is hereby extended to [**].

Sections 10.2 ("*Governing Law*") and 10.3 ("*Submission to Jurisdiction*") of the Agreement are hereby incorporated herein by reference.

Acknowledged, Agreed, and Confirmed

/s/ Daniel Tassé	/s/ Kinneret Savitsky
Daniel Tassé Chief Executive Officer Ikaria Development Subsidiary One LLC	Kinneret Savitsky, Chief Executive Officer ***On behalf of, and as authorized representative of, both BioLineRx Ltd. and BioLine Innovations Jerusalem L.P.***

AMENDMENT TO THE AMENDED AND RESTATED LICENSE AND COMMERCIALIZATION AGREEMENT

This Amendment (this "Amendment") is entered into this 21st day of April 2010 (the "Amendment Effective Date") by and between **Ikaria Development Subsidiary One LLC**, a Delaware limited liability company with a place of business at 6 Route 173, Clinton, NJ, 08809 USA ("Ikaria"), and **BiolineRx Ltd.**, a corporation organized and existing under the laws of the State of Israel and having a principal place of business at 19 Hartum Street, P.O. Box 45158, Jerusalem 91450, Israel ("BioLineRx Ltd."), and **BioLine Innovations Jerusalem L.P.**, a limited partnership organized and existing under the laws of the State of Israel and having a principal place of business at 19 Hartum Street, P.O. Box 45158 Jerusalem 91450, Israel ("BioLine Innovations"; together with BioLineRx Ltd., "BioLine Rx") . This Amendment amends the Amended and Restated License and Commercialization Agreement entered into by and between Ikaria and BioLineRx dated as of the 26th day of August 2009 (the "Agreement"). Any defined term used in this Amendment not expressly defined herein shall have the meaning ascribed thereto in the Agreement.

1. Modification of Payee. All payments to be made under the Agreement shall be made to BiolineRx Ltd. or any Third Party assignee of BioLineRx Ltd. permitted under Section 10.4 of the Agreement.

2. Modification of Assignment. The last two sentences of Section 10.4 of the Agreement are hereby amended and restated as follows:

> "BioLineRx Ltd. may assign its right to receive payments hereunder to a Third Party, in its sole discretion, provided that BioLineRx Ltd. provides Ikaria with prior written notice of the assignment and the name and address of the assignee. Any such Third Party assignee may not further assign the right to receive payments hereunder without providing Ikaria with prior written notice of the assignment and the name and address of the assignee. Ikaria shall maintain a written record of any such assignments. The parties intend that this Agreement shall be considered to be in "registered form" as defined in United States Treasury Regulations Section 5f.103-1(c). BiolineRx shall not otherwise be permitted to assign this Agreement, in whole or in part, without the prior written consent of Ikaria, which approval shall not be unreasonably withheld, conditioned, or delayed. Any assignment in contravention of this Section 10.4 shall be null and void."

3. Ratification of Agreement. Except as set forth in this Amendment, all of the other terms and conditions of the Agreement are hereby ratified and confirmed to be of full force and effect, and shall continue in full force and effect. This Amendment is hereby integrated into and made a part of the Agreement.

4. Counterparts. This Amendment may be executed in two or more counterparts, each of which shall be effective as of the Amendment Effective Date, and all of which shall constitute one and the same instrument. Each such counterpart shall be deemed an original, and it shall not be necessary in making proof of this Amendment to produce or account for more than one such counterpart.

5. Execution and Delivery. This Amendment shall be deemed executed by the parties when any one or more counterparts hereof, individually or taken together, bears the signatures of each of the parties hereto.

Acknowledged and Agreed to:

BIOLINERX LTD.

By: /s/ Kinneret L. Savitsky /s/ Philip Serlin
Signature

Kinneret L. Savitsky Philip Serlin
Printed Name

CEO CFO
Title

April 21, 2010

IKARIA DEVELOPMENT SUBSIDIARY ONE LLC

By: /s/ Matthew M. Bennett
Signature

Matthew M. Bennett
Printed Name

Vice President and Secretary
Title

April 21, 2010

BIOLINE INNOVATIONS JERUSALEM L.P., BY ITS GENERAL PARTNER BIOLINE INNOVATIONS JERUSALEM, LTD.

By: /s/ Kinneret L. Savitsky /s/ Philip Serlin
Signature

Kinneret L. Savitsky Philip Serlin
Printed Name

CEO CFO
Title

April 21, 2010

Execution copy

AMENDMENT
TO
AMENDED AND RESTATED LICENSE AND COMMERCIALIZATION AGREEMENT

Amendment to Amended and Restated License and Commercialization Agreement (this "Amendment"), dated as of January 8, 2015 (the "Amendment Effective Date"), by and among Bellerophon BCM LLC, a Delaware limited liability company formerly known as Ikaria Development Subsidiary One LLC ("Bellerophon"), on the one hand, and BioLineRx Ltd., a corporation organized and existing under the laws of the State of Israel ("BioLineRx"), on the other hand. Each of Bellerophon and BioLineRx may be referred to herein as a "Party" and Bellerophon and BioLineRx may be referred to herein collectively as the "Parties."

WHEREAS, Bellerophon, BioLineRx and BioLine Innovations Jerusalem L.P., a limited partnership organized and existing under the laws of the State of Israel ("BioLine Innovations") entered into an Amended and Restated License and Commercialization Agreement as of August 26, 2009 (the "Agreement");

WHEREAS, BioLine Innovations has assigned all of its rights and obligations under the Agreement to BioLineRx, and BioLineRx has assumed such rights and obligations;

WHEREAS, Bellerophon has consented to the foregoing assignment and assumption in accordance with Section 10.4 of the Agreement;

WHEREAS, BioLineRx has alleged certain breaches or potential breaches of the Agreement in correspondence to Bellerophon, and Bellerophon has denied that any breach of the Agreement exists; and

WHEREAS, the Parties desire to amend certain provisions of the Agreement and to resolve all disputes relating to the Agreement that have arisen between them;

NOW, THEREFORE, in consideration of the premises and the mutual covenants contained herein, and for other good and valuable consideration, the Parties, intending to be legally bound, hereby agree as follows:

1. **Definitions.** Capitalized terms used but not otherwise defined herein shall have the meanings ascribed to such terms in the Agreement. For the avoidance of doubt, Bellerophon, as defined in this Amendment, and Ikaria, as defined in the Agreement, are one and the same entity.

2. **Amendment to Agreement Terms**. Section 4.1(a)(3) of the Agreement is hereby amended and restated to read as follows:

"
[**]

"

3. **Release**. BioLineRx, on its own behalf and on behalf of its predecessors, successors, assigns, affiliates, agents and representatives, and each of them in all of their capacities, shall, and hereby does (in such capacity, the "Releasing Parties"), forever waive, release and discharge Bellerophon and Bellerophon's affiliates, and its and their predecessors, successors, assigns, affiliates, agents, representatives, officers, directors, employees, stockholders, attorneys and advisors, and each of them in all of their capacities (in such capacity, the "Released Parties"), of and from any and all claims, causes of

action, demands, damages, debts, liabilities, obligations, equitable and provisional remedies, costs, expenses (including attorneys' and accountants' fees and expenses) actions and causes of action of any nature whatsoever, whether now known or unknown, suspected or unsuspected, that such Releasing Party now has or at any time previously had, based in any way, directly or indirectly, on the Agreement or the spin-out of Bellerophon from Ikaria Holdings, Inc. and its affiliates, or based on any act or failure to act, or on any disclosure or failure to disclose, by Bellerophon under or in connection with the Agreement (each, a "Claim"). Each Releasing Party irrevocably covenants and agrees not to assert directly or indirectly any Claim, or to commence, institute or cause to be commenced, any proceeding of any kind against any of the Released Parties, based upon, regarding, related to or arising out of any matters released in this release, and further covenants and agrees that this Amendment is a bar to any such Claim.

4. **Miscellaneous**. The Parties hereby confirm and agree that, as amended hereby, the provisions of the Agreement shall remain unchanged and in full force and effect and the Agreement remains a binding obligation of the Parties. This Amendment may be executed in counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. Facsimile signatures and signatures transmitted via PDF shall be treated as original signatures. Headings used herein are for convenience only and shall not in any way affect the construction of or be taken into consideration in interpreting the Agreement.

IN WITNESS WHEREOF, the Parties have caused this Amendment to be executed by their duly authorized representatives.

BELLEROPHON BCM LLC		**BIOLINERX LTD.**	
By:	/s/ Jonathan Peacock	By:	/s/ Kinneret Savitsky /s/ Philip Serlin
Name:	Jonathan Peacock	Name:	Kinneret Savitsky Philip Serlin
Title:	Chief Executive Officer	Title:	CEO CFO/COO

Exhibit 10.16

REGISTRATION RIGHTS AGREEMENT

This REGISTRATION RIGHTS AGREEMENT, dated as of February 12, 2015, is made and entered into by and among (i) Bellerophon Therapeutics, Inc., a Delaware corporation (formerly Bellerophon Therapeutics LLC, a Delaware limited liability company), (ii) New Mountain Partners II (AIV-A), L.P., a Delaware limited partnership ("**NMP II-A**"), New Mountain Partners II (AIV-B), L.P., a Delaware limited partnership ("**NMP II-B**"), New Mountain Affiliated Investors II, L.P., a Delaware limited partnership ("**NMAI**"), and Allegheny New Mountain Partners, L.P., a Delaware limited partnership ("**ANMP**" and, collectively with NMP II-A, NMP II-B and NMAI, the "**NMP Entities**"), (iii) ARCH Venture Fund VI, L.P., a Delaware limited partnership ("**ARCH**"), (iv) Venrock Partners, L.P., a Delaware limited partnership, Venrock Associates IV, L.P., a Delaware limited partnership, and Venrock Entrepreneurs Fund IV, L.P., a Delaware limited partnership (collectively, the "**Venrock Entities**"), (v) Linde North America, Inc., a Delaware corporation ("**Linde**"), (vi) 5AM Ventures LLC, a Delaware limited liability company, and 5AM Co-Investors LLC, a Delaware limited liability company (together, the "**5AM Entities**"), (vii) Aravis Venture I L.P., a Cayman Islands limited partnership ("**Aravis**" and, together with the NMP Entities, ARCH, the Venrock Entities, Linde and the 5AM Entities, the "**Investors**"), and (viii) such other Holders who are signatories hereto or who become signatories hereto from time to time as provided for herein. Capitalized terms shall have the meanings assigned to them in Section 1.

WHEREAS, the Company is party to a Registration Rights Agreement, dated as of February 12, 2014, with (i) NMP II-A, NMAI and ANMP, (ii) IRDO Holding Corp., a Delaware corporation (and an Affiliate of ARCH) ("**ARCH Blocker**"), (iii) Venrock IK Holdings BT, Inc., a Delaware corporation (and an Affiliate of the Venrock Entities) ("**Venrock Blocker**"), (iv) Linde, (v) 5AM-BT, Inc., a Delaware corporation (and an Affiliate of the 5AM Entities) ("**5AM Blocker**"), and (vi) Aravis (the "**Original Registration Rights Agreement**");

WHEREAS, Section 14.01 of the Amended and Restated Limited Liability Company Agreement of Bellerophon Therapeutics LLC, dated as of February 9, 2014, provides that, concurrently with a conversion of Bellerophon Therapeutics LLC from a limited liability company into a corporation, the successor corporation shall enter into a registration rights agreement in a form substantially similar to, and which shall replace, the Original Registration Rights Agreement;

WHEREAS, in anticipation of its initial public offering, Bellerophon Therapeutics LLC has been converted on the date hereof from a limited liability company into a corporation known as Bellerophon Therapeutics, Inc. and, in connection therewith, each of New Mountain Partners II Special (AIV-A), L.P., a Delaware limited partnership (and an Affiliate of NMP II-A), ARCH Blocker, Venrock Blocker and 5AM Blocker have been merged with and into Bellerophon Therapeutics, Inc.; and

WHEREAS, in light of the foregoing, the parties have agreed to enter into this Agreement to provide the parties with the rights and obligations set forth in this Agreement.

NOW, THEREFORE, in consideration of the premises and the mutual agreements contained herein, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto hereby agree as follows:

SECTION. 1. Defined Terms.

1.1. Definitions. For purposes of this Agreement, the following terms have the following meanings:

"**Affiliate**" means (a) with respect to any Person, any other Person which, directly or indirectly, controls, is controlled by or is under common control with such Person, where "**control**" means the possession, directly or indirectly, of the power to direct the management and policies of such Person, whether through the ownership of voting securities, by contract or otherwise, and (b) with respect to any individual, also means the spouse or child of such individual.

"**Agreement**" means this Registration Rights Agreement, as the same may be amended, restated, modified or supplemented from time to time.

"**Beneficially Own**" means beneficially own as determined under Rule 13d-3 promulgated under the Exchange Act.

"**Board**" means the board of directors of the Company as it may be composed from time to time in accordance with the Certificate of Incorporation, the Company's bylaws (as in effect from time to time), the Voting Agreement, dated as of February 12, 2014, by and among the Company and the Investors, as the same may be amended, restated, modified or supplemented from time to time, the Stockholders Agreement and the General Corporation Law of the State of Delaware (as in effect from time to time).

"**Business Day**" means any day excluding Saturday, Sunday and any day which is a legal holiday under the laws of the State of New York, or is a day on which banking institutions located in New York, New York are authorized or required by law or other governmental action to close.

"**Certificate of Incorporation**" means the Certificate of Incorporation of the Company, as in effect from time to time.

"**Common Stock**" means any shares of common stock, par value $0.01 per share, of the Company, now or hereafter authorized to be issued, and any and all Equity Interests of any kind whatsoever of the Company which may be issued on or after the date hereof in respect of, in exchange for, or upon conversion of Common Stock pursuant to a merger, consolidation, stock split, reverse split, stock dividend, recapitalization of the Company or otherwise.

"**Company**" means Bellerophon Therapeutics, Inc., a Delaware corporation, and shall, to the extent this Agreement survives, include any successor thereto by merger, consolidation, acquisition of substantially all the assets thereof, or otherwise, including any parent or subsidiary thereof that undertakes a Public Offering in lieu of the Company.

"**Convertible Securities**" means (a) any options or warrants to purchase or other rights to acquire Common Stock, (b) any securities by their terms convertible into, or exercisable or exchangeable for, Common Stock (directly or indirectly) and (c) any options or warrants to purchase or other rights to acquire any such convertible, exercisable or exchangeable securities.

"**Counsel to the Participating Holders**" means one (1) law firm selected by the Majority Participating Holders.

"**Equity Interests**" of any Person means any and all units, shares, participations or other equivalents of or interests in (however designated) the equity (including common stock, preferred stock and limited liability company, partnership and joint venture interests) of such Person.

"**Exchange Act**" means the Securities Exchange Act of 1934, as amended from time to time, or any similar federal statute, and the rules and regulations of the SEC thereunder, all as the same shall be in effect at the time. Reference to a particular section of the Exchange Act shall include a reference to the comparable section, if any, of any such similar federal statute.

"**FINRA**" means the Financial Industry Regulatory Authority, Inc. or any successor Person.

"**Holder**" means, at any time of determination, (a) any Investor, (b) any Permitted Assignee of any Investor or other Holder, or (c) any other Person (i) that has acquired Common Stock, (ii) that the Company and Holders holding in the aggregate at least 50% of the outstanding Registrable Securities then held by the Holders consent in writing to becoming a party to this Agreement and (iii) that has executed and delivered a written agreement (which may be in the form of a counterpart signature page or joinder to this Agreement) satisfactory to the Company agreeing to be bound by this Agreement as a Holder, in each case of clauses (a), (b) and (c) only if such Person holds Common Stock at such time.

"**indemnified party**" means any Person seeking indemnification pursuant to Section 2.6.

"**indemnifying party**" means any Person from whom indemnification is sought pursuant to Section 2.6.

"**Initial Public Offering**" means the first Public Offering.

"**Initiating Holder**" means the Holder or Holders delivering a Holder Demand as provided for under Section 2.1(a).

"**Majority Participating Holders**" means, at any time, Participating Holders holding more than fifty percent (50%) of the Registrable Securities proposed to be included in any offering of Registrable Securities by such Participating Holders pursuant to Section 2.1 or 2.2.

"**NMP Holders**" means, at any time of determination, any of the NMP Entities that hold Common Stock at such time.

"**Participating Holders**" means any Holder or Holders participating in any offering of Registrable Securities pursuant to Section 2.1 or 2.2.

"**Person**" means any individual, corporation, association, partnership (general or limited), joint venture, trust, estate, limited liability company, organization or other legal entity.

"**Pre-IPO Certificate of Incorporation**" means the Certificate of Incorporation of the Company, as in effect immediately prior to an Initial Public Offering.

"**Public Offering**" means a public offering of Equity Interests of the Company through a registration statement (except registrations (i) solely for registration of Equity Interests of the Company in connection with an employee benefit plan or dividend reinvestment plan on Form S-8 or any successor form thereto or (ii) in connection with any acquisition, merger or other business combination transaction on Form S-4 or any successor form thereto) filed with, and declared effective by, the SEC and pursuant to which such Equity Interests are authorized and approved for listing on a national securities exchange.

"**Quarterly Outstanding Common Stock**" means, at any time of determination, (a) if such time is prior to the consummation of an Initial Public Offering, the number of shares of Common Stock that were outstanding on the last day of the immediately preceding fiscal quarter (including any shares of Common Stock issuable upon conversion or exercise of or in exchange for any Convertible Securities to the extent any such Convertible Securities are (i) convertible, exercisable or exchangeable at such time and (ii) convertible, exercisable or exchangeable at a price that is less than the fair market value (as determined by the Board in good faith) of a share of Common Stock issuable upon such conversion, exercise or exchange at such time) and (b) if such time is after the consummation of an Initial Public Offering, the number of shares of Common Stock that were set forth as outstanding on the cover of the Company's then most recently filed Annual Report on Form 10-K or Quarterly Report on Form 10-Q, as the case may be.

"**Registrable Securities**" means any Common Stock held by a Holder. For purposes of this Agreement, a Person will be deemed to be a Holder of Registrable Securities whenever such Person has the right to acquire, directly or indirectly, such Registrable Securities (including upon conversion, exercise or exchange of any Convertible Securities but disregarding any restrictions or limitations upon the exercise of such right), whether or not such acquisition has actually been effected, and such Person shall not be required to convert, exercise or exchange such Convertible Securities (or otherwise acquire such Registrable Securities) to participate in any registered offering hereunder until the closing of such offering. As to any particular

Registrable Securities, such securities shall cease to be Registrable Securities when (a) a registration statement with respect to the sale of such securities shall have become effective under the Securities Act and such securities shall have been disposed of in accordance with such registration statement, (b) such securities shall have been sold to the public pursuant to Rule 144, or (c) such securities shall have ceased to be outstanding.

"**Registration Expenses**" means all fees and expenses incurred in connection with the Company's performance of or compliance with Section 2, including (a) all registration, filing and applicable SEC fees, FINRA fees, national securities exchange or inter-dealer quotation system fees, foreign stock exchange fees, and fees and expenses of complying with state, federal or foreign securities or "blue sky" laws (including fees and disbursements of counsel to the underwriters and Counsel to the Participating Holders in connection with "blue sky" or foreign qualification of the Registrable Securities and determination of their eligibility for investment under the laws of the various jurisdictions), (b) all printing (including printing certificates for the Registrable Securities (if they are to be certificated) in a form eligible for deposit with The Depository Trust Company and printing preliminary and final prospectuses or other offering documents), word processing, duplicating, telephone and facsimile expenses, and messenger and delivery expenses, (c) all fees and disbursements of counsel to the Company and of its independent public accountants, including the expenses of "cold comfort" letters or any special audits required by, or incidental to, such registration, (d) all fees and expenses of Counsel to the Participating Holders, (e) all fees and expenses of one (1) firm of accountants selected by the Majority Participating Holders, (f) all fees and expenses of any special experts or other Persons retained by the Company in connection with any registration, (g) Securities Act liability insurance or similar insurance if the Company so desires or the underwriters so require in accordance with then-customary underwriting practices, (h) all applicable rating agency fees with respect to the Registrable Securities, (i) all fees and expenses of a "Qualified Independent Underwriter" (as such term is defined by FINRA) and its counsel or similar fees and expenses, (j) all fees and disbursements of the underwriters (other than underwriting discounts and commissions), (k) all transfer taxes and (l) all expenses incurred in connection with promotional efforts or "roadshows"; provided that Registration Expenses shall exclude, and the Participating Holders shall pay, underwriting discounts and commissions in respect of the Registrable Securities being registered for such Participating Holders.

"**Requisite Approval**" means the approval of the Board and the NMP Entities in accordance with the terms of the Stockholders Agreement.

"**Rule 144**" means Rule 144 promulgated under the Securities Act.

"**SEC**" means the United States Securities and Exchange Commission or any other federal agency at the time administering the Securities Act.

"**Securities Act**" means the Securities Act of 1933, as amended from time to time, or any similar federal statute, and the rules and regulations of the SEC thereunder, all as the same shall be in effect at the time. References to a particular section of the Securities Act shall include a reference to the comparable section, if any, of any such similar federal statute.

"**Stockholders Agreement**" means the Stockholders Agreement, dated as of , 2015, by and among the Company and the NMP Entities, as the same may be amended, restated, modified or supplemented from time to time.

"**Tag-Along Holder**" means (i) a holder of Tag-Along Securities on the date of this Agreement that has the right to participate in an Initial Public Offering with respect to such Tag-Along Securities pursuant to the Pre-IPO Certificate of Incorporation or (ii) any Permitted Transferee (as defined in the Pre-IPO Certificate of Incorporation) of any Tag-Along Holder that holds Tag-Along Securities.

"**Tag-Along Securities**" means any Common Stock subject to restrictions on transfer under the Pre-IPO Certificate of Incorporation (but not any Common Stock held by a Holder). For purposes of this Agreement, a Person will be deemed to be a holder of Tag-Along Securities whenever such Person has the right to acquire, directly or indirectly, such Tag-Along Securities (including upon conversion, exercise or exchange of any Convertible Securities), whether or not such acquisition has actually been effected, and such Person shall not be required to convert, exercise or exchange such Convertible Securities (or otherwise acquire such Tag-Along Securities) to participate in any registered offering hereunder until the closing of such offering. As to any particular Tag-Along Securities, such securities shall cease to be Tag-Along Securities upon the earliest of (a) the closing of an Initial Public Offering, (b) such time as Rule 144 or another similar exemption under the Securities Act is available for the sale of all of the Tag-Along Securities held by such Tag-Along Holder without limitation during a three-month period without registration or (c) the time at which such securities shall have ceased to be outstanding.

"**Ten Percent Holder**" means, at any time of determination, any Holder or Holders that hold at least ten percent (10%) in the aggregate of the Quarterly Outstanding Common Stock.

1.2. Other Defined Terms. The following is a list of the remaining defined terms used in this Agreement:

Term	Section
5AM Blocker	Recitals
5AM Entities	Preamble
ANMP	Preamble
Aravis	Preamble
ARCH	Preamble
ARCH Blocker	Recitals
automatic shelf registration statement	2.1(l)
Demand Exercise Notice	2.1(a)
Demand Registration	2.1(i)
Holder Demand	2.1(a)
Indemnitees	2.6(a)
Investors	Preamble

Linde	Preamble
Losses	2.6(a)
NASDAQ	2.3(a)(x)
NMAI	Preamble
NMP Entities	Preamble
NMP II-A	Preamble
NMP II-B	Preamble
Original Registration Rights Agreement	Recitals
Partner Distribution	2.1(a)
Permitted Assignee	4.10
Postponement Period	2.1(k)
Section 2.2 Sale Amount	2.2(d)
Venrock Blocker	Recitals
Venrock Entities	Preamble
WKSI	2.1(l)

SECTION. 2. Registration Under Securities Act.

2.1. Registration on Demand.

(a) Demand. At any time (subject to the provisions of Section 3 of the Stockholders Agreement) or from time to time, an NMP Holder (or a Permitted Assignee of an NMP Holder to the extent permitted by Section 4.10 hereof) holding Registrable Securities or, at any time from and after an Initial Public Offering, a Ten Percent Holder holding Registrable Securities, may require the Company to effect the registration under the Securities Act of all or part of their Registrable Securities, by delivering a written request (a "**Holder Demand**") therefor to the Company specifying the number of Registrable Securities to be registered and the intended method of distribution thereof. As promptly as practicable, but no later than ten (10) Business Days after receipt of a Holder Demand, the Company shall give written notice (the "**Demand Exercise Notice**") of the Holder Demand to all other Holders. Each such other Holder shall have the option, within ten (10) Business Days after the receipt of the Demand Exercise Notice (or five (5) Business Days if, at the request of the Initiating Holder, the Company states in such written notice or gives telephonic notice to each Holder, with written confirmation to follow promptly thereafter, that (i) such registration will be on Form S-3 and (ii) such shorter period of time is required because of a planned filing date) to request, in writing, that the Company include in such registration any Registrable Securities held by such Holder (which request shall specify the maximum number of Registrable Securities desired to be disposed of by such Holder). The Company shall as expeditiously as possible (but in any event within eighty (80) Business Days after receipt of a Holder Demand with respect to an Initial Public Offering and within sixty (60) Business Days otherwise) use its reasonable best efforts to effect the registration under the Securities Act of the Registrable Securities which the Company has been so requested to register by the Initiating Holder and by any other Holders which have made such written request. The Company shall (i) use its reasonable best efforts to effect the registration of Registrable Securities for distribution in accordance with the intended method of distribution set forth in a written request delivered by the Majority Participating Holders, which may include, at the option of such Majority Participating Holders, a distribution of Registrable

Securities to, and resale of such Registrable Securities by, the equity holders of any Holder or its equity holders (a "**Partner Distribution**"), and (ii) if requested by the Majority Participating Holders, obtain acceleration of the effective date of the registration statement relating to such registration.

(b) Partner Distributions. Notwithstanding anything contained herein to the contrary, the Company shall, at the request of any Participating Holder seeking to effect a Partner Distribution, file any prospectus supplement or post-effective amendments and shall otherwise take any action necessary to include such language, if such language was not included in the initial registration statement, or revise such language if deemed necessary by such Participating Holder, to effect such Partner Distribution (including adding one or more selling equity holders to the registration statement through a prospectus supplement or post-effective amendment, as necessary or required).

(c) Registration Statement Form. Registrations under this Section 2.1 shall be on such appropriate form of the SEC (i) as shall be selected by the Majority Participating Holders and as shall be reasonably acceptable to the Company and (ii) as shall permit the disposition of such Registrable Securities in accordance with the intended method or methods of disposition specified in such Participating Holders' requests for such registration, including a Partner Distribution or a continuous or delayed basis offering pursuant to Rule 415 under the Securities Act. The Company agrees to include in any such registration statement all information which, in the opinion of Counsel to the Participating Holders and counsel to the Company, is necessary or desirable to be included therein.

(d) Expenses. The Company shall pay, and shall be responsible for, all Registration Expenses in connection with any registration requested pursuant to this Section 2.1, regardless of whether the registration is effected, except as set forth in clause (v) of Section 2.1(e) with respect to a registration statement that was withdrawn at the request of the Participating Holders. Notwithstanding the foregoing, the provisions of this Section 2.1(d) shall be deemed amended to the extent necessary to cause these expense provisions to comply with "blue sky" laws of each state or the securities laws of any other jurisdiction in the United States and its territories or any foreign jurisdiction in which the offering is made.

(e) Effective Registration Statement. A registration requested pursuant to this Section 2.1 shall not be deemed a Demand Registration (including for purposes of Section 2.1(i)) unless a registration statement with respect thereto has become effective and has been kept continuously effective for a period of at least one hundred eighty (180) days (or such shorter period which shall terminate when all the Registrable Securities covered by such registration statement have been sold pursuant thereto) or, if such registration statement relates to an underwritten offering, such longer period as in the opinion of Counsel to the Participating Holders or counsel to the underwriter or underwriters a prospectus is required by law to be delivered in connection with sales of Registrable Securities by an underwriter or dealer. Should a Demand Registration not become effective due to the failure of a Participating Holder to perform its obligations under this Agreement, or in the event the Majority Participating Holders withdraw the request for the Demand Registration as provided for in Section 2.1(h) (in each of the foregoing cases, provided that at such time the Company is in compliance in all material

respects with its obligations under this Agreement), then such Demand Registration shall be deemed to have been effected (including for purposes of Section 2.1(i)); provided that, if (i) the Demand Registration is withdrawn or does not become effective because a material adverse change has occurred, or is reasonably likely to occur, in the condition (financial or otherwise), prospects, business, assets or results of operations of the Company and its subsidiaries taken as a whole subsequent to the date of the delivery of the Demand Exercise Notice, (ii) after the Demand Registration has become effective, such registration is interfered with by any stop order, injunction, or other order or requirement of the SEC or other governmental agency or court, (iii) the Demand Registration is withdrawn at the request of the Majority Participating Holders due to the advice of the managing underwriter(s) that the Registrable Securities covered by the registration statement could not be sold in such offering within a price range acceptable to the Majority Participating Holders, (iv) the Demand Registration is withdrawn for any reason at any time during a Postponement Period or within ten (10) days thereafter, or (v) the Participating Holders reimburse the Company for any and all Registration Expenses incurred by the Company in connection with such request for a Demand Registration that was withdrawn for reasons other than any of those enumerated in clauses (i) through (iv) of this Section 2.1(e), then the Demand Registration shall not be deemed to have been effected and will not count as a Demand Registration.

(f) Selection of Underwriters. The underwriters of each underwritten offering of the Registrable Securities pursuant to this Section 2.1 shall be selected by the Majority Participating Holders.

(g) Tag-Along Securities. Following receipt of a Holder Demand with respect to any proposed Initial Public Offering, the Company shall give any Tag-Along Holders notice thereof, and shall include in such offering any Tag-Along Securities as to which the Tag-Along Holders are entitled to, and have elected to, participate (as though they were Registrable Securities), pursuant to and in accordance with the Pre-IPO Certificate of Incorporation and this Section 2.1.

(h) Right to Withdraw. Any Participating Holder shall have the right to withdraw its request for inclusion of Registrable Securities in any registration statement pursuant to this Section 2.1 by giving written notice to the Company of its request to withdraw at any time prior to the effective date of such registration statement or otherwise in accordance with the process established in connection with the offering. Upon receipt of notices from the Majority Participating Holders to such effect, the Company shall cease all efforts to obtain effectiveness of the applicable registration statement, and whether the Initiating Holder's request for registration pursuant to this Section 2.1 shall be counted as a Demand Registration for purposes of Section 2.1(i) shall be determined in accordance with Section 2.1(e).

(i) Limitations on Registration on Demand. The Company shall be required to effect eight (8) registrations in the aggregate pursuant to this Section 2.1, other than registrations on Form S-3, which shall not be subject to this limitation, of which (i) the NMP Holders (or the Permitted Assignees of the NMP Holders to the extent permitted by Section 4.10 hereof) shall be entitled to require the Company to effect six (6) registrations in the aggregate, including for an Initial Public Offering, and (ii) after an Initial Public Offering, the Ten Percent

Holders shall be entitled to require the Company to effect two (2) registrations in the aggregate (each, a "**Demand Registration**"); provided that the Company shall not be required to effect a Demand Registration until at least ninety (90) days after the effective date of any other registration statement filed by the Company pursuant to a previous Demand Registration. The aggregate offering value of the Registrable Securities to be registered pursuant to any Demand Registration shall be at least $10 million (determined as of the date the demand is made), unless the registration is of the balance of the Registrable Securities held by all the Holders.

(j) Priority in Registrations on Demand. Whenever the Company effects a registration pursuant to this Section 2.1 in connection with an underwritten offering by Holders, no securities other than Registrable Securities and Tag-Along Securities shall be included among the securities covered by such registration unless the Majority Participating Holders consent in writing to the inclusion therein of such other Equity Interests of the Company, which consent may be subject to terms and conditions determined by the Majority Participating Holders in their sole discretion. If any registration pursuant to a Holder Demand involves an underwritten offering and the managing underwriter(s) of such offering shall inform the Company of its belief that the number of Registrable Securities requested to be included in such registration pursuant to this Section 2.1, when added to the number of any other Equity Interests of the Company to be offered in such registration (including any Tag-Along Securities), exceeds the largest number that can be sold in an orderly manner in such underwritten offering within a price range acceptable to the Majority Participating Holders, then the Participating Holders and Tag-Along Holders shall be entitled to participate on a pro rata basis based on the aggregate number of Registrable Securities and Tag-Along Securities (treating them as a single class of securities) requested to be included in the offering by each such Participating Holder and Tag-Along Holder (but in the case of any Tag-Along Holder, not in excess of the number of Tag-Along Securities with respect to which such Tag-Along Holder is entitled to participate pursuant to the terms of the Pre-IPO Certificate of Incorporation).

(k) Postponement. The Company shall be entitled once in any twelve (12) month period to postpone for a reasonable period of time (but not exceeding ninety (90) days) (the "**Postponement Period**") the filing of any registration statement required to be prepared and filed by it pursuant to this Section 2.1 if the Company determines, in its reasonable judgment upon advice of counsel, as authorized by a resolution of its Board, that such registration and offering would require premature disclosure of any material financing, acquisition, corporate reorganization, business combination or other material transaction involving the Company or any of its subsidiaries, and promptly gives the Participating Holders written notice of such determination, containing a statement of the reasons for such postponement and an approximation of the anticipated delay; provided, however, that the Company shall be entitled to postpone the filing of any registration statement required to be prepared and filed by it pursuant to this Section 2.1 if such postponement is required by applicable law arising from events outside of the control of the Company.

(l) WKSI.

(i) To the extent the Company is a well-known seasoned issuer (as defined in Rule 405 under the Securities Act) (a "**WKSI**") at the time any Holder Demand is

submitted to the Company, and such Holder Demand requests that the Company file an automatic shelf registration statement (as defined in Rule 405 under the Securities Act) (an "**automatic shelf registration statement**") on Form S-3, the Company shall file an automatic shelf registration statement which covers those Registrable Securities which are requested to be registered. The Company shall use commercially reasonable efforts to remain a WKSI (and not become an ineligible issuer (as defined in Rule 405 under the Securities Act)) during the period during which such automatic shelf registration statement is required to remain effective. If the Company does not pay the filing fee covering the Registrable Securities at the time the automatic shelf registration statement is filed, the Company shall pay such fee at such time or times as the Registrable Securities are to be sold. If the automatic shelf registration statement has been outstanding for at least three (3) years, at the end of the third year the Company shall refile a new automatic shelf registration statement covering the Registrable Securities. If at any time when the Company is required to re-evaluate its WKSI status the Company determines that it is not a WKSI, the Company shall use commercially reasonable efforts to refile the shelf registration statement on Form S-3 and, if such form is not available, Form S-1 and keep such registration statement effective during the period during which such registration statement is required to be kept effective.

(ii) If the Company files any shelf registration statement for the benefit of the holders of any of its securities other than the Holders, the Company agrees that it shall include in such registration statement such disclosures as may be required by Rule 430B under the Securities Act (referring to the unnamed selling security holders in a generic manner by identifying the initial offering of the securities to the Holders) in order to ensure that the Holders may be added to such shelf registration statement at a later time through the filing of a prospectus supplement rather than a post-effective amendment.

2.2. Incidental Registration.

(a) Right to Include Registrable Securities. If the Company at any time proposes to register any of its Equity Interests under the Securities Act by registration on Form S-1 or S-3, or any successor or similar form(s) (except registrations (i) pursuant to Section 2.1, (ii) in connection with an Initial Public Offering that is approved by the NMP Entities and in which no NMP Entity is selling Registrable Securities, (iii) solely for registration of Equity Interests of the Company in connection with an employee benefit plan or dividend reinvestment plan on Form S-8 or any successor form thereto or (iv) in connection with any acquisition, merger or other business combination transaction on Form S-4 or any successor form thereto), whether or not for sale for the Company's own account, the Company will each such time give prompt written notice (but in no event less than thirty (30) days prior to the effectiveness of a registration statement with respect thereto) to each of the Holders of its intention to do so and such notice shall offer the Holders of such Registrable Securities the opportunity to register under such registration statement up to such number of Registrable Securities as each such Holder may request in writing. Upon the written request of any of the Holders (which request shall specify the maximum number of Registrable Securities intended to be disposed of by such Holder), within ten (10) Business Days after the receipt of any such notice (or within five (5) Business Days if the Company states in such written notice or gives telephonic notice to each Holder, with written confirmation to follow promptly thereafter, stating that (i) such registration will be on

Form S-3 and (ii) such shorter period of time is required because of a planned offering date), the Company shall include in such registration under the Securities Act all Registrable Securities which the Company has been so requested to register by each Holder; provided that if, at any time after giving written notice of its intention to register any Equity Interests of the Company and prior to the effective date of the registration statement filed in connection with such registration, the Company shall determine for any reason not to register or to delay registration of such Equity Interests, the Company shall give written notice of such determination and its reasons therefor to the Holders and (i) in the case of a determination not to register, shall be relieved of its obligation to register any Registrable Securities in connection with such registration (but not from any obligation of the Company to pay the Registration Expenses in connection therewith as provided for in Section 2.2(e)), without prejudice, however, to the rights of the Holders to request that such registration be effected as a registration under Section 2.1 and (ii) in the case of a determination to delay registering, shall be permitted to delay registering any Registrable Securities for the same period as the delay in registering such other Equity Interests of the Company. No registration effected under this Section 2.2 shall relieve the Company of its obligation to effect any registration upon request under Section 2.1.

(b) Tag-Along Securities. In the case of an Initial Public Offering with respect to which the Company receives a written request from an NMP Holder (or a Permitted Assignee of an NMP Holder) to include Registrable Securities in such registration in connection with the exercise of such NMP Holder's (or such Permitted Assignee's) registration rights under Section 2.2(a) hereof, the Company shall give any Tag-Along Holders notice thereof, and shall include in such offering any Tag-Along Securities as to which the Tag-Along Holders are entitled to, and have elected to, participate (as though they were Registrable Securities), pursuant to and in accordance with the Pre-IPO Certificate of Incorporation.

(c) Right to Withdraw; Option to Participate in Shelf Takedowns. Any Holder shall have the right to withdraw its request for inclusion of Registrable Securities in any registration statement pursuant to this Section 2.2 by giving written notice to the Company of its request to withdraw at any time prior to the effective date of such registration statement or otherwise in accordance with the process established in connection with the offering. In the event that the Holder has requested inclusion of Registrable Securities in a shelf registration, the Holder shall have the right, but not the obligation, to participate in any offering of the Company's Equity Interests under such shelf registration.

(d) Priority in Incidental Registrations. If any registration pursuant to this Section 2.2 involves an underwritten offering and the managing underwriter(s) of such offering shall inform the Company of its belief that the number of Registrable Securities requested to be included in such registration or offering, when added to the number of other Equity Interests of the Company to be offered in such registration or offering (including any Tag-Along Securities) exceeds the largest number that can be sold in an orderly manner in such underwritten offering within a price range acceptable to the Majority Participating Holders (the "**Section 2.2 Sale Amount**"), then the Company shall include in such registration or offering (i) all of the Equity Interests of the Company proposed by the Company to be sold for its own account; (ii) thereafter, to the extent the Section 2.2 Sale Amount is not exceeded, the Registrable Securities and Tag-Along Securities requested by the Participating Holders and Tag-Along Holders (provided that if

all of the Registrable Securities and Tag-Along Securities requested by the Participating Holders and Tag-Along Holders may not be included, the Participating Holders and Tag-Along Holders shall be entitled to participate on a pro rata basis based on the aggregate number of Registrable Securities and Tag-Along Securities (treating them as a single class of securities) requested to be included in the offering by the Participating Holders and Tag-Along Holders (but, in the case of any Tag-Along Holder, not in excess of the number of Tag-Along Securities with respect to which such Tag-Along Holder is entitled to participate pursuant to the terms of the Pre-IPO Certificate of Incorporation); and (iii) thereafter, to the extent the Section 2.2 Sale Amount is not exceeded, any other Equity Interests of the Company requested to be included by holders of Equity Interests of the Company holding other such registration rights.

(e) Expenses. The Company shall pay, and shall be responsible for, all Registration Expenses in connection with any registration requested pursuant to this Section 2.2. Notwithstanding the foregoing, the provisions of this Section 2.2(e) shall be deemed amended to the extent necessary to cause these expense provisions to comply with "blue sky" laws of each state or the securities laws of any other jurisdiction in the United States and its territories or any foreign jurisdiction in which the offering is made.

(f) Selection of Underwriters. The underwriters of each underwritten offering which may include Registrable Securities pursuant to this Section 2.2 shall be selected by the Majority Participating Holders; provided that such underwriters shall be reasonably acceptable to the Company.

(g) Plan of Distribution; Partner Distributions. Any participation by Holders in a registration by the Company shall be in accordance with the Company's plan of distribution, which shall include, upon the written request of such Holder or Holders, a Partner Distribution. Notwithstanding anything contained herein to the contrary, the Company shall, at the request of any Holder seeking to effect a Partner Distribution, file any prospectus supplement or post-effective amendments and otherwise take any action necessary to include such language, if such language was not included in the initial registration statement, or revise such language if deemed reasonably necessary by such Holder to effect such Partner Distribution.

2.3. Registration Procedures.

(a) If and whenever the Company is required to effect the registration of any Registrable Securities under the Securities Act pursuant to either Section 2.1 or 2.2, the Company shall as expeditiously as possible:

(i) prepare and file, or confidentially submit, if permissible, with the SEC as promptly as practicable (and in the case of a demand pursuant to Section 2.1, within forty-five (45) days after receipt by the Company of a Demand Exercise Notice) a registration statement on an appropriate registration form of the SEC for the disposition of such Registrable Securities in accordance with the intended method of disposition thereof (including a Partner Distribution) which registration statement shall comply as to form in all material respects with the requirements of the applicable form and include all financial statements required by the SEC to be filed therewith, and thereafter use its reasonable best efforts to cause such registration

statement to become and remain effective (A) with respect to an underwritten offering, for a period of at least one hundred eighty (180) days or until all Registrable Securities subject to such registration statement have been sold, and (B) with respect to a shelf registration, until the later of (1) the sale of all Registrable Securities thereunder and (2) the third anniversary of the effective date of such shelf registration;

(ii) prepare and file with the SEC any amendments and supplements to such registration statement and the prospectus used in connection therewith, or any free writing prospectus related thereto, as may be necessary to keep such registration statement effective and to comply with the provisions of the Securities Act with respect to the disposition of all Registrable Securities covered by such registration statement in accordance with the intended methods of disposition by the Participating Holders set forth in such registration statement for such period as provided for in Section 2.3(a)(i);

(iii) furnish, without charge, to each Participating Holder and each underwriter such number of conformed copies of such registration statement and of each such amendment and supplement thereto (in each case including all exhibits), such number of copies of the prospectus contained in such registration statement (including each preliminary prospectus and summary prospectus) and any other prospectus filed under Rule 424 under the Securities Act, in conformity with the requirements of the Securities Act, each free writing prospectus utilized in connection therewith, and such other documents, as the Majority Participating Holders and such underwriters may request (it being understood that the Company consents to the use of such prospectus or any amendment or supplement thereto or free writing prospectus by each Participating Holder and the underwriters in connection with the offering and sale of the Registrable Securities covered by such prospectus or any amendment or supplement thereto);

(iv) use its reasonable best efforts (A) to register or qualify all Registrable Securities and other Equity Interests of the Company covered by such registration statement under such state, federal or foreign securities or "blue sky" laws where an exemption is not available and as the Majority Participating Holders or any managing underwriter shall request, (B) to keep such registration or qualification in effect for so long as such registration statement remains in effect, and (C) to take any and all other actions which may be necessary or advisable to enable the Participating Holders or underwriters to consummate the disposition in such jurisdictions of the Equity Interests of the Company to be sold by the Participating Holders or underwriters, except that the Company shall not for any such purpose be required to qualify generally to do business as a foreign corporation in any jurisdiction wherein it would not, but for the requirements of this Section 2.3(a)(iv), be obligated to be so qualified;

(v) use its reasonable best efforts to cause all Registrable Securities covered by such registration statement to be registered with or approved by such other local, state, federal, or foreign governmental agencies or authorities as may be necessary in the opinion of counsel to the Company and Counsel to the Participating Holders to consummate the disposition of such Registrable Securities;

(vi) use its reasonable best efforts to furnish to each Participating Holder and each underwriter a signed counterpart of (A) an opinion of counsel to the Company and (B) a "comfort" letter signed by the independent public accountants who have certified the Company's financial statements included or incorporated by reference in such registration statement, in each case, addressed to each Participating Holder and each underwriter covering matters with respect to such registration statement (and the prospectus included therein) as such Majority Participating Holders and managing underwriter(s) shall request;

(vii) promptly notify each Participating Holder and each managing underwriter (A) when such registration statement, any pre-effective amendment, the prospectus or any prospectus supplement related thereto, any post-effective amendment to such registration statement or any free writing prospectus has been filed and/or used and, with respect to such registration statement or any post-effective amendment, when the same has become effective; (B) of the receipt by the Company of any comments from the SEC or receipt of any request by the SEC for additional information with respect to any registration statement or the prospectus related thereto or any request by the SEC for amending or supplementing the registration statement and the prospectus used in connection therewith; (C) of the issuance by the SEC of any stop order suspending the effectiveness of such registration statement or the initiation of any proceedings for that purpose; (D) of the receipt by the Company of any notification with respect to the suspension of the qualification of any of the Registrable Securities for sale under the securities or "blue sky" laws of any jurisdiction or the initiation of any proceeding for such purpose; (E) at any time when a prospectus relating thereto is required to be delivered under the Securities Act, upon discovery that, or upon the happening of any event as a result of which, the prospectus included in such registration statement, any document incorporated therein by reference, any free writing prospectus or information conveyed to any purchaser, as then in effect, includes an untrue statement of a material fact or omits to state any material fact required to be stated therein or necessary to make the statements therein not misleading, in the light of the circumstances under which they were made, and in the case of this clause (E), promptly prepare and furnish, at the Company's expense, to each Participating Holder and each managing underwriter a number of copies of a supplement to or an amendment of such prospectus as may be necessary so that, as thereafter delivered to the purchasers of such Equity Interests of the Company, such prospectus shall not include an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made; (F) at any time when the representations and warranties of the Company contemplated by Section 2.4(a) or 2.4(b) cease to be true and correct; and (G) of the Company's filing of a document pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act that, in the reasonable judgment of the Company, must be included in the registration statement pursuant to a post-effective amendment to the registration statement or supplement to the related prospectus, and in the case of this clause (G), promptly prepare and furnish, at the Company's expense, to each Participating Holder and each managing underwriter copies of a supplement to or an amendment of such prospectus on account of such Exchange Act filing;

(viii) otherwise comply with all applicable rules and regulations of the SEC, and make available to each Participating Holder, as soon as practicable (and in any event within sixteen (16) months after the effective date of the registration statement), an

earnings statement covering the period of at least twelve (12) consecutive months beginning with the first full calendar month after the effective date of such registration statement, which earnings statement shall satisfy the provisions of Section 11(a) of the Securities Act and Rule 158 promulgated thereunder;

(ix) provide and cause to be maintained a transfer agent and registrar for all Registrable Securities covered by such registration statement from and after a date not later than the effective date of such registration statement;

(x) (A) use its reasonable best efforts to cause all Registrable Securities covered by such registration statement to be listed on the principal securities exchange on which similar Equity Interests of the Company are then listed (if any), if the listing of such Registrable Securities is then permitted under the rules of such exchange, or (B) if no such similar Equity Interests are then so listed, use its reasonable best efforts to (1) cause all such Registrable Securities to be listed on a national securities exchange, (2) secure designation of all such Registrable Securities as a National Association of Securities Dealers, Inc. Automated Quotation System ("**NASDAQ**") "national market system security" within the meaning of Rule 11Aa2-1 of the SEC, or (3) failing that, to secure NASDAQ authorization for such shares and, without limiting the generality of the foregoing, to arrange for at least two market makers to register as such with respect to such shares with FINRA;

(xi) deliver promptly to Counsel to the Participating Holders and each underwriter, if any, participating in the offering of the Registrable Securities, copies of all correspondence between the SEC and the Company, its counsel or auditors and all memoranda relating to discussions with the SEC or its staff with respect to such registration statement;

(xii) use its reasonable best efforts to obtain the withdrawal of any order suspending the effectiveness of the registration statement;

(xiii) provide a CUSIP number for all Registrable Securities no later than the effective date of the registration statement and provide the applicable transfer agents with printed certificates for the Registrable Securities which are in a form eligible for deposit with The Depository Trust Company;

(xiv) cause its officers and employees to participate in, and to otherwise facilitate and cooperate with, the preparation of the registration statement and prospectus and any amendments or supplements thereto (including participating in meetings, drafting sessions, due diligence sessions and the marketing of the Registrable Securities covered by the registration statement (including participation in "road shows") taking into account the Company's business needs);

(xv) enter into and perform its obligations under such customary agreements (including, if applicable, an underwriting agreement as provided for in Section 2.4) and take such other actions as the Majority Participating Holders or managing underwriter(s) shall request in order to expedite or facilitate the disposition of such Registrable Securities;

(xvi) promptly incorporate in a prospectus supplement or post-effective amendment such information as the managing underwriter(s) or Majority Participating Holders request to be included therein relating to the plan of distribution with respect to such Registrable Securities; and make all required filings of such prospectus supplement or post-effective amendment as soon as practicable after being notified of the matters to be incorporated in such prospectus supplement or post-effective amendment;

(xvii) cooperate with each Participating Holder and each underwriter, and their respective counsel in connection with any filings required to be made with FINRA, the New York Stock Exchange, the Nasdaq National Market, or any other securities exchange on which such Registrable Securities are traded or will be traded;

(xviii) promptly prior to the filing of any document which is to be incorporated by reference into the registration statement or the prospectus contained therein (after the initial filing of such registration statement), and prior to the filing or use of any free writing prospectus, provide copies of such document to Counsel to the Participating Holders and to each managing underwriter, and make the Company's representatives available for discussion of such document and make such changes in such document concerning the Participating Holders prior to the filing thereof as Counsel to the Participating Holders or underwriters may request;

(xix) furnish to each Participating Holder and each managing underwriter, without charge, at least one (1) signed copy of the registration statement and any post-effective amendments thereto, including financial statements and schedules, all documents incorporated therein by reference and all exhibits (including those incorporated by reference) and any free writing prospectus utilized in connection therewith;

(xx) cooperate with the Participating Holders and the managing underwriter(s) to facilitate the timely preparation and delivery of certificates not bearing any restrictive legends representing the Registrable Securities to be sold, and cause such Registrable Securities to be issued in such denominations and registered in such names in accordance with the underwriting agreement prior to any sale of Registrable Securities to the underwriters or, if not an underwritten offering, in accordance with the instructions of the Participating Holders at least five (5) Business Days prior to any sale of Registrable Securities and instruct any transfer agent or registrar of Registrable Securities to release any stop transfer orders in respect thereof;

(xxi) to the extent required by the rules and regulations of FINRA, retain a Qualified Independent Underwriter, which shall be acceptable to the Majority Participating Holders;

(xxii) take no direct or indirect action prohibited by Regulation M under the Exchange Act; provided that to the extent that any prohibition is applicable to the Company, the Company will take all reasonable action to make any such prohibition inapplicable;

(xxiii) take all reasonable action to ensure that any free writing prospectus utilized in connection with any registration covered by Section 2.1 or 2.2 complies in

all material respects with the Securities Act, is filed in accordance with the Securities Act to the extent required thereby, is retained in accordance with the Securities Act to the extent required thereby and, when taken together with the related prospectus, prospectus supplement and related documents, will not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements therein, in light of the circumstances under which they were made, not misleading;

(xxiv) in connection with any underwritten offering (whether or not off of a shelf registration statement), if at any time the information conveyed to a purchaser at the time of sale includes any untrue statement of a material fact or omits to state any material fact necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading, promptly file with the SEC such amendments or supplements to such information as may be necessary so that the statements as so amended or supplemented will not, in light of the circumstances, be misleading; and

(xxv) in connection with any underwritten offering (whether or not off of a shelf registration statement), if the Company files a document pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act that, in the reasonable judgment of the Company, must be included in the registration statement pursuant to a post-effective amendment to the registration statement or supplement to the related prospectus, promptly file with the SEC such amendments or supplements to such information as may be necessary on account of such Exchange Act filing.

(b) Each Participating Holder agrees that upon receipt of any notice from the Company of the happening of any event of the kind described in clause (C), (E) or (G) of Section 2.3(a)(vii), each Participating Holder will, to the extent appropriate, discontinue its disposition of Registrable Securities pursuant to the registration statement relating to such Registrable Securities until, in the case of clause (C) of Section 2.3(a)(vii), its receipt of notice from the Company that such stop order or suspension of effectiveness is no longer in effect, and in the case of clauses (E) and (G) of Section 2.3(a)(vii), its receipt of the copies of the supplemented or amended prospectus contemplated by clause (E) or (G) of Section 2.3(a)(vii) and, if so directed by the Company, will deliver to the Company (at the Company's expense) all copies, other than permanent file copies, then in its possession, of the prospectus relating to such Registrable Securities current at the time of receipt of such notice. If the disposition by a Participating Holder of its Registrable Securities is discontinued pursuant to the foregoing sentence, the Company shall extend the period of effectiveness of the registration statement by the number of days during the period from and including the date of the giving of such notice to and including the date when the Participating Holder shall have received (in the case of clause (C) of Section 2.3(a)(vii)) notice that such stop order or suspension of effectiveness is no longer in effect, and (in the case of clauses (E) and (G) of Section 2.3(a)(vii)) copies of the supplemented or amended prospectus contemplated by clause (E) or (G) of Section 2.3(a)(vii); and, if the Company shall not so extend such period, the Participating Holder's request pursuant to which such registration statement was filed shall not be counted for purposes of the requests for registration to which the Participating Holder is entitled pursuant to Section 2.1. If for any other reason the effectiveness of any registration statement filed pursuant to Section 2.1 or 2.2 is suspended or interrupted prior to the expiration of the time period regarding the maintenance of

the effectiveness of such registration statement required by Section 2.3(a)(i) so that Registrable Securities may not be sold pursuant thereto, the applicable time period shall be extended by the number of days equal to the number of days during the period beginning with the date of such suspension or interruption to and ending with the date when the sale of Registrable Securities pursuant to such registration statement may be resumed.

(c) If any such registration statement or comparable statement under "blue sky" laws refers to any Holder by name or otherwise as the holder of any Equity Interests of the Company, then such Holder shall have the right to require (i) the insertion therein of language, in form and substance satisfactory to such Holder and the Company, to the effect that the holding by such Holder of such Equity Interests is not to be construed as a recommendation by such Holder of the investment quality of the Company's Equity Interests covered thereby and that such holding does not imply that such Holder will assist in meeting any future financial requirements of the Company, or (ii) in the event that such reference to such Holder by name or otherwise is not in the judgment of the Company, as advised by counsel, required by the Securities Act or any similar federal statute or any state or foreign "blue sky" or securities law then in force, the deletion of the reference to such Holder.

(d) Holders may seek to register different types of Registrable Securities simultaneously and the Company shall use its reasonable best efforts to effect such registration and sale in accordance with the intended method or methods of disposition specified by such Holders.

(e) In connection with an underwritten offering related to a shelf take-down, the Company will comply with all of these registration procedures as reasonably appropriate in the opinion of the Majority Participating Holders.

2.4. Underwritten Offerings.

(a) Demand Underwritten Offerings. If requested by the underwriters for any underwritten offering by the Participating Holders pursuant to a registration requested under Section 2.1, the Company shall enter into a customary underwriting agreement with the managing underwriter(s) selected by the Majority Participating Holders pursuant to Section 2.1(f). Such underwriting agreement shall be reasonably satisfactory in form and substance to the Majority Participating Holders and the Company and shall contain such representations and warranties by, and such other agreements on the part of, the Company and such other terms as are generally prevailing in agreements of that type, including customary provisions relating to indemnification and contribution which are no less favorable to the recipient than those provided in Section 2.6. Each Participating Holder shall be a party to such underwriting agreement. The Majority Participating Holders may, at their option, require that any or all of the representations and warranties by, and the other agreements on the part of, the Company to and for the benefit of such underwriters shall also be made to and for the benefit of each Participating Holder and that any or all of the conditions precedent to the obligations of such underwriters under such underwriting agreement be conditions precedent to the obligations of each Participating Holder; provided that the Company shall not be required to make any representations or warranties with respect to written information specifically provided by a

Participating Holder for inclusion in the registration statement. No Participating Holder shall be required to make any representations or warranties to or agreements with the Company or the underwriters other than representations, warranties or agreements regarding such Participating Holder, its ownership of and title to the Registrable Securities, its intended method of distribution, and disclosures related to the foregoing; and any liability of any Participating Holder to any underwriter or other Person under such underwriting agreement shall be limited to liability arising from breach of its representations and warranties and shall be limited to an amount equal to the proceeds (net of expenses and underwriting discounts and commissions) that it derives from such registration, except in the case of willful fraud by such Participating Holder.

(b) Incidental Underwritten Offerings. In the case of a registration pursuant to Section 2.2, if the Company shall have determined to enter into an underwriting agreement in connection therewith, all of the Registrable Securities to be included in such registration shall be subject to such underwriting agreements. The Majority Participating Holders may, at their option, require that any or all of the representations and warranties by, and the other agreements on the part of, the Company to and for the benefit of such underwriters shall also be made to and for the benefit of the Participating Holders and that any or all of the conditions precedent to the obligations of such underwriters under such underwriting agreement be conditions precedent to the obligations of the Participating Holders; provided that the Company shall not be required to make any representations or warranties with respect to written information specifically provided by a Participating Holder for inclusion in the registration statement. None of the Participating Holders shall be required to make any representations or warranties to or agreements with the Company or the underwriters other than representations, warranties or agreements regarding such Participating Holder, its ownership of and title to the Registrable Securities, its intended method of distribution and disclosures related to the foregoing; and any liability of any Participating Holder to any underwriter or other Person under such underwriting agreement shall be limited to liability arising from breach of its representations and warranties and shall be limited to an amount equal to the proceeds (net of expenses and underwriting discounts and commissions) that it derives from such registration, except in the case of willful fraud by such Participating Holder.

(c) Participation in Underwritten Registrations. In the case of an underwritten registration pursuant to Section 2.1 or 2.2, as the Company may from time to time reasonably request in writing, the Company may require the Participating Holders (i) to furnish the Company such information regarding such Participating Holders and the distribution of the Registrable Securities to enable the Company to comply with the requirements of applicable laws or regulations in connection with such registration and (ii) to complete and execute all customary questionnaires, powers of attorney, indemnities, underwriting agreements and other documents reasonably required under the terms of such underwriting arrangements. The Company shall not be obligated to effect the registration of any Registrable Securities of a particular Participating Holder unless such information and documents regarding such Participating Holder and the distribution of such Participating Holder's Registrable Securities is provided to the Company.

2.5. Preparation; Reasonable Investigation. In connection with the preparation and filing of each registration statement under the Securities Act pursuant to this Agreement, the Company will give the Participating Holders, the managing underwriter(s), and their respective

counsel, accountants and other representatives and agents the opportunity to participate in the preparation of such registration statement, each prospectus included therein or filed with the SEC, and each amendment thereof or supplement thereto or comparable statements under securities or "blue sky" laws of any jurisdiction, and give each of the foregoing parties access to its books and records, all financial and other records, pertinent corporate documents and properties of the Company and its subsidiaries, and such opportunities to discuss the business of the Company and its subsidiaries with their respective directors, officers and employees and the independent public accountants who have certified the Company and its subsidiaries' financial statements, and supply all other information and respond to all inquiries requested by such Participating Holders, managing underwriter(s), or their respective counsel, accountants or other representatives or agents in connection with such registration statement, as shall be necessary or appropriate, in the opinion of counsel to such Participating Holder or managing underwriter(s), to conduct a reasonable investigation within the meaning of the Securities Act, and the Company shall not file any registration statement or amendment thereto or any prospectus or supplement thereto to which the Majority Participating Holders or the managing underwriter(s) shall object.

2.6. Indemnification.

(a) Indemnification by the Company. The Company agrees that in the event of any registration of any Registrable Securities under the Securities Act, the Company shall, and hereby does, indemnify and hold harmless, to the fullest extent permitted by law, (i) each of the Holders and their respective Affiliates, (ii) each of the Holders' and their Affiliates' respective Affiliates, officers, directors, successors, assigns, members, partners, equity holders, employees, advisors, and agents, (iii) each other Person who participates as an underwriter or Qualified Independent Underwriter in the offering or sale of such Equity Interests and their respective directors, officers and Affiliates, (iv) each Person who controls (within the meaning of the Securities Act or the Exchange Act) any of the Persons listed in clauses (i), (ii) or (iii), and (v) any representative (legal or otherwise) of any of the Persons listed in clauses (i), (ii), (iii) or (iv) (collectively, the "**Indemnitees**"), from and against any losses, penalties, fines, liens, judgments, suits, claims, damages, liabilities, costs and expenses (including attorney's fees and any amounts paid in any settlement effected in compliance with Section 2.6(e)) or liabilities, joint or several (or actions or proceedings, whether commenced or threatened, in respect thereof, and whether or not such Indemnitee is a party thereto) ("**Losses**"), to which such Indemnitee has become or may become subject under the Securities Act or otherwise, insofar as such Losses arise out of, relate to or are based upon (A) any untrue statement or alleged untrue statement of any material fact contained in any registration statement under which such Equity Interests were registered under the Securities Act, any preliminary prospectus, final prospectus or summary prospectus contained therein, any amendment or supplement thereto, any documents incorporated by reference therein, or any free writing prospectus or road show utilized in connection therewith, (B) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, (C) any untrue statement or alleged untrue statement of a material fact in the information conveyed to any purchaser at the time of the sale to such purchaser, or the omission or alleged omission to state therein a material fact required to be stated therein, or (D) any violation by the Company of any federal, state or common law rule or regulation applicable to the Company and relating to action required of or inaction by the Company in connection with any such registration, and the Company shall reimburse such

Indemnitee for its legal and other fees and expenses incurred by it in connection with investigating or defending any such Loss; provided that the Company shall not be liable to an Indemnitee to the extent that any such Loss arises out of or is based upon an untrue statement or alleged untrue statement or omission or alleged omission made in any such registration statement, any such preliminary prospectus, final prospectus or summary prospectus, any amendment or supplement thereto or document incorporated by reference therein, or any such free writing prospectus or road show, in reliance upon and in conformity with written information furnished to the Company by or on behalf of such Indemnitee, which specifically states that it is for use in the preparation of such registration statement, preliminary prospectus, final prospectus, summary prospectus, amendment, supplement, document or free writing prospectus.

(b) Indemnification by Participating Holders. As a condition to including any Registrable Securities in any registration statement, the Company shall have received an undertaking reasonably satisfactory to it from each Participating Holder so including any Registrable Securities to, severally and not jointly, indemnify and hold harmless, to the fullest extent permitted by law, (i) the Company, each director and officer of the Company, and each other Person, if any, who controls the Company within the meaning of the Securities Act or Exchange Act and (ii) any underwriters of the Registrable Securities, their officers and directors and each Person who controls such underwriters (within the meaning of the Securities Act or the Exchange Act) and their Affiliates, from and against any Losses to which such indemnified parties have become or may become subject under the Securities Act or otherwise, insofar as such Losses arise out of, relate to or are based upon any statement or alleged statement in or omission or alleged omission from such registration statement, any preliminary prospectus, final prospectus or summary prospectus contained therein, any amendment or supplement thereto, or any free writing prospectus or road show utilized in connection therewith, but only to the extent such statement or alleged statement or omission or alleged omission was made in reliance upon and in conformity with written information furnished by such Participating Holder to the Company which specifically states that it is for use in the preparation of such registration statement, any preliminary prospectus, final prospectus or summary prospectus contained therein, any amendment or supplement thereto, or any free writing prospectus or road show utilized in connection therewith, and such Participating Holder shall reimburse such indemnified party for any reasonable legal or any other fees or expenses reasonably incurred by them in connection with investigating or defending any such Loss; provided that the aggregate liability of such indemnifying party under this Section 2.6(b) shall be limited to the amount of proceeds (net of expenses and underwriting discounts and commissions) received by such indemnifying party in the offering giving rise to such liability, except in the case of willful fraud by such Participating Holder. Each Participating Holder shall also indemnify and hold harmless all other prospective sellers and Participating Holders, their respective Affiliates, officers, directors, successors, assigns, members, partners, equity holders, employees, advisors, representatives (legal or otherwise), and agents, and each Person who controls (within the meaning of the Securities Act or the Exchange Act) any such seller or Participating Holder to the same extent as provided above with respect to indemnification of the Company and underwriters.

(c) Notices of Claims. Promptly after receipt by an indemnified party of notice of the commencement of any action or proceeding involving a claim referred to in

Section 2.6(a) or 2.6(b), such indemnified party shall, if a claim in respect thereof is to be made against an indemnifying party, give written notice to such indemnifying party of the commencement of such action or proceeding; provided that the failure of any indemnified party to give notice as provided herein shall not relieve the indemnifying party of its obligations under Section 2.6(a) or 2.6(b), except to the extent that the indemnifying party is actually and materially prejudiced by such failure to give notice, and shall not relieve the indemnifying party from any liability which it may have to the indemnified party otherwise than under this Section 2.6.

(d) Defense of Claims. In case any such action or proceeding is brought against an indemnified party, except as provided for in the next sentence, the indemnifying party shall be entitled to participate therein and assume the defense thereof, jointly with any other indemnifying party, with counsel reasonably satisfactory to such indemnified party, and after notice from the indemnifying party to such indemnified party of its election so to assume the defense thereof and approval by the indemnified party of such counsel, the indemnifying party shall not be liable to such indemnified party for any legal expenses subsequently incurred by such indemnified party in connection with the defense thereof other than costs of investigation, and the indemnified party shall be entitled to participate in such defense at its own expense. If (i) the indemnifying party fails to notify the indemnified party in writing, within fifteen (15) days after the indemnified party has given notice of the action or proceeding, that the indemnifying party will indemnify the indemnified party from and against all Losses the indemnified party may suffer resulting from, arising out of, relating to, in the nature of, or caused by the claim, (ii) the indemnifying party fails to provide the indemnified party with evidence acceptable to the indemnified party that the indemnifying party will have the financial resources to defend against the claim or proceeding and fulfill its indemnification obligations hereunder, (iii) after electing to participate in and assume the defense of such action or proceeding, the indemnifying party fails to defend diligently the action or proceeding within ten (10) Business Days after receiving notice of such failure from such indemnified party; (iv) such indemnified party reasonably shall have concluded (upon advice of its counsel) that there may be one or more legal defenses available to such indemnified party or other indemnified parties which are not available to the indemnifying party; or (v) if such indemnified party reasonably shall have concluded (upon advice of its counsel) that, with respect to such claims, the indemnified party and the indemnifying party may have different, conflicting, or adverse legal positions or interests then, in any such case, the indemnified party shall have the right to assume or continue its own defense and the indemnifying party shall be liable for any fees and expenses therefor.

(e) Consent to Entry of Judgment and Settlements. No indemnifying party shall be liable for any settlement of any action or proceeding effected without its written consent, which consent shall not be unreasonably withheld, delayed or conditioned, provided that, in the case where the indemnifying party shall have failed to take any of the actions listed in clauses (i), (ii) or (iii) of the last sentence of Section 2.6(d), the indemnified party shall have the right to compromise or settle such action on behalf of and for the account, expense, and risk of the indemnifying party and the indemnifying party will remain responsible for any Losses the indemnified party may suffer resulting from, arising out of, relating to, in the nature of, or caused by the action or proceeding to the fullest extent provided in this Section 2.6. No indemnifying party shall, without the written consent of the indemnified party, effect the settlement or compromise of, or consent to the entry of any judgment with respect to, any pending or

threatened action or claim in respect of which indemnification or contribution may be sought hereunder (whether or not the indemnified party is an actual or potential party to such action or claim) unless such settlement, compromise or judgment (A) includes an unconditional release of the indemnified party from all liability arising out of such action or claim, (B) does not include a statement as to or an admission of fault, culpability or a failure to act, by or on behalf of any indemnified party and (C) does not require any action other than the payment of money by the indemnifying party.

(f) Contribution. If for any reason the indemnification provided for in Section 2.6(a), 2.6(b) or 2.6(g) is unavailable to an indemnified party or insufficient in respect of any Losses referred to therein, then, in lieu of the amount paid or payable under Section 2.6(a), 2.6(b) or 2.6(g), the indemnifying party shall contribute to the amount paid or payable by the indemnified party as a result of such Loss (i) in such proportion as is appropriate to reflect the relative fault of the indemnifying party on the one hand, and the indemnified party on the other hand, with respect to the statements or omissions which resulted in such Loss, as well as any other relevant equitable considerations, or (ii) if the allocation provided by clause (i) is not permitted by applicable law or if the allocation provided in this clause (ii) provides a greater amount to the indemnified party than clause (i), in such proportion as shall be appropriate to reflect not only the relative fault but also the relative benefits received by the indemnifying party and the indemnified party from the offering of the Equity Interests of the Company covered by such registration statement as well as any other relevant equitable considerations. The relative fault shall be determined by a court of competent jurisdiction with reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the indemnifying party or the indemnified party and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such untrue statement or omission. The parties hereto agree that it would not be just and equitable if contributions pursuant to this Section 2.6(f) were to be determined by pro rata allocation or by any other method of allocation which does not take into account the equitable considerations referred to in the preceding sentence of this Section 2.6(f). No Person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any Person who was not guilty of such fraudulent misrepresentation. The amount paid or payable by an indemnified party as a result of the Losses referred to in Section 2.6(a), 2.6(b) or 2.6(g) shall be deemed to include, subject to the limitations set forth in Sections 2.6(a), 2.6(b) and 2.6(g), any legal or other expenses reasonably incurred by such indemnified party in connection with investigating or defending any such action or claim. Notwithstanding anything in this Section 2.6(f) to the contrary, no Participating Holder shall be required to contribute any amount in excess of the proceeds (net of expenses and underwriting discounts and commissions) received by such Participating Holder from the sale of the Registrable Securities in the offering to which the Losses of the indemnified parties relate, except in the case of willful fraud by such Participating Holder.

(g) Other Indemnification. Indemnification and contribution similar to that specified in the preceding subsections of this Section 2.6 (with appropriate modifications) shall be given by the Company and the Participating Holders with respect to any required registration or other qualification of Equity Interests of the Company under any state, federal or foreign securities or "blue sky" laws. The indemnification agreements contained in this Section 2.6

shall be in addition to any other rights to indemnification or contribution which any indemnified party may have pursuant to law or contract and shall remain operative and in full force and effect regardless of any investigation made by or on behalf of any Indemnitee or other indemnified party and shall survive the transfer of any of the Registrable Securities by any such party.

(h) Indemnification Payments. The indemnification and contribution required by this Section 2.6 shall be made by periodic payments of the amount thereof during the course of the investigation or defense, as and when bills are received or a Loss is incurred.

2.7. Limitation on Sale of Equity Interests.

(a) For the Company and Others. If the Company receives a request for registration pursuant to an underwritten offering of Registrable Securities pursuant to Section 2.1 or 2.2 or if a shelf take-down is being undertaken, and if such a request is being implemented or has not been withdrawn or abandoned, the Company agrees that (i) the Company shall not effect any public or private offer, sale, distribution or other disposition of any Registrable Securities or Convertible Securities or effect any registration of any of its Equity Interests under the Securities Act (in each case, other than (u) as part of such registration, (v) any Equity Interests issued by the Company upon the exercise of an option or warrant or the conversion of an Equity Interest, but only to the extent that (A) such option, warrant or Equity Interest was outstanding on the date hereof or (B) the grant or issuance of such option, warrant or Equity Interest received the Requisite Approval, (w) any Equity Interests issued or granted pursuant to equity incentive plans, including any non-employee director stock plan, the adoption of which plan received the Requisite Approval and which issuance or grant received the Requisite Approval; (x) any Equity Interests issued pursuant to any dividend reinvestment plan, the adoption of which plan received the Requisite Approval; (y) the filing by the Company of any registration statement on Form S-8 or a successor form thereto; and (z) any Equity Interests issued in connection with a transaction that includes a commercial relationship (including joint ventures or other strategic acquisitions), which transaction received the Requisite Approval), whether or not for sale for its own account, during the period beginning on the date the Company receives such request and ending one hundred eighty (180) days after the effective date of such registration in the case of the Initial Public Offering or ninety (90) days after the effective date of such registration in the case of any other underwritten Public Offering, plus, in each case, any customary extension periods (or such shorter period as the managing underwriter(s) may require), and (ii) the Company shall use its reasonable best efforts to obtain from each of its officers, directors and Persons who Beneficially Own five percent (5%) or more of the Company's Equity Interests, an agreement not to effect any public or private offer, sale, distribution or other disposition of Equity Interests of the Company, or any Equity Interests of the Company that are convertible into or exchangeable or exercisable for other Equity Interests of the Company, including a sale pursuant to Rule 144, during the one hundred eighty (180) day period in the case of an Initial Public Offering (or such shorter period as the managing underwriter(s) may require), or the ninety (90) day period in the case of any other underwritten Public Offering (or such shorter period as the managing underwriter(s) may require), in each case beginning on the effective date of such registration statement.

(b) For the Holders. If the Company receives a request for registration pursuant to an underwritten offering of Registrable Securities pursuant to Section 2.1 or 2.2 or if

a shelf take-down is being undertaken (and if such a request is being implemented or has not been withdrawn or abandoned), each Holder agrees that, to the extent requested in writing by the managing underwriter(s), it will not effect any public or private offer, sale, distribution or other disposition of any Registrable Securities or Convertible Securities (other than as a part of such registration), including a sale pursuant to Rule 144, during the one hundred eighty (180) day period in the case of an Initial Public Offering (or such shorter period as the managing underwriter(s) may require), or the ninety (90) day period in the case of any other underwritten Public Offering (or such shorter period as the managing underwriter(s) may require), in each case beginning on the effective date of such registration statement or the closing of the shelf take-down plus any customary extension periods; provided that each Holder has received the written notice required by Section 2.1(a) or 2.2(a), as applicable; and provided, further, that in connection with such underwritten offering each officer and director of the Company is subject to restrictions substantially equivalent to those imposed on the Holders.

2.8. No Required Sale. Nothing in this Agreement shall be deemed to create an independent obligation on the part of any of the Holders to sell any Registrable Securities pursuant to any effective registration statement.

2.9. Rule 144; Rule 144A; Regulation S. The Company covenants that, at its own expense, it will file the reports required to be filed by it under the Securities Act and the Exchange Act, and it will take such further action as any Holder may reasonably request, all to the extent required from time to time to enable such Holder to sell Registrable Securities without registration under the Securities Act within the limitations of the exemptions provided by (a) Rule 144, Rule 144A or Regulation S under the Securities Act or (b) any similar rule or regulation hereafter adopted by the SEC. Upon the request of a Holder, the Company, at its own expense, will promptly deliver to such Holder (i) a written statement as to whether it has complied with such requirements (and such Holder shall be entitled to rely upon the accuracy of such written statement), (ii) a copy of the most recent annual or quarterly report of the Company and (iii) such other reports and documents as such Holder may reasonably request in order to avail itself of any rule or regulation of the SEC allowing it to sell any Registrable Securities without registration.

2.10. Adjustments. At the request of Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders, in the event of any change in the capitalization of the Company as a result of any stock split, stock dividend, reverse split, combination, conversion, recapitalization, merger, consolidation or otherwise, the provisions of this Section 2 shall be appropriately adjusted. The Company agrees that it shall not effect or permit to occur any combination or subdivision of its Equity Interests which would adversely affect the ability of the Holders to include any Registrable Securities in any registration contemplated by this Agreement or the marketability of such Registrable Securities in any such registration. The Company agrees that it will take all steps necessary to effect a combination or subdivision of its Equity Interests if, in the judgment of Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders or the managing underwriter(s), such combination or subdivision would enhance the marketability of the Registrable Securities.

SECTION. 3. Subsequent Registration Rights; No Inconsistent Agreements.

3.1. Limitations on Subsequent Registration Rights. From and after the date of this Agreement until the Holders and their respective Permitted Assignees shall no longer hold any Registrable Securities, without the prior written consent of Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders, the Company shall not enter into an agreement that grants a holder or prospective holder of any Equity Interests of the Company demand or incidental registration rights. Notwithstanding the foregoing, if, after the date of this Agreement, the Company enters into any other agreement with respect to the registration of any of its Equity Interests, and the terms contained therein are more favorable to, or less restrictive on, the other party thereto than the terms and conditions contained in this Agreement (insofar as they are applicable) with respect to the Holders, then, at the request of Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders, the terms of this Agreement shall immediately be deemed to have been amended without further action by the Company or the Holders so that the Holders shall be entitled to the benefit of any such more favorable or less restrictive terms or conditions.

3.2. No Inconsistent Agreements. Without the prior written consent of Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders, the Company will not, on or after the date of this Agreement, enter into any agreement with respect to its Equity Interests which is inconsistent with the rights granted to the Holders in Section 2 or otherwise conflicts with the provisions of Section 2, other than any customary lock-up agreement with the underwriters in connection with any offering effected hereunder, pursuant to which the Company shall agree not to register for sale, and the Company shall agree not to sell or otherwise dispose of, Equity Interests of the Company or any Convertible Securities, for a specified period (not to exceed one hundred eighty (180) days plus customary extension periods) following such offering. The Company represents and warrants that the rights granted to the Holders hereunder do not in any way conflict with and are not inconsistent with any other agreements to which the Company is a party or by which it is bound. The Company is not bound by any agreement with respect to its Equity Interests granting any registration rights to any Person.

SECTION. 4. Miscellaneous.

4.1. Rules of Construction.

(a) An accounting term not otherwise defined herein has the meaning assigned to it in accordance with U.S. GAAP;

(b) References in the singular or to “him,” “her,” “it,” “itself,” or other like references, and references in the plural or the feminine or masculine or neutral reference, as the case may be, shall also, when the context so requires, be deemed to include the plural or singular, or the masculine or feminine or neutral reference, as the case may be;

(c) References to Sections shall refer to sections of this Agreement, unless otherwise specified;

(d) The headings in this Agreement are for convenience and identification only and are not intended to describe, interpret, define or limit the scope, extent or intent of this Agreement or any provision hereof;

(e) This Agreement shall be construed without regard to any presumption or other rule requiring construction against the party that drafted and caused this Agreement to be drafted;

(f) References to "days" shall refer to calendar days unless Business Days are specified. If any period expires on a day which is not a Business Day or any event or condition is required by the terms of this Agreement to occur or be fulfilled on a day which is not a Business Day, such period shall expire or such event or condition shall occur or be fulfilled, as the case may be, on the next succeeding Business Day;

(g) Any action required to be taken "within" a specified time period following the occurrence of an event shall be required to be taken no later than 5:00 PM, Eastern time, on the last day of the time period, which shall be calculated starting with the day immediately following the date of the event;

(h) All monetary figures shall be in United States dollars unless otherwise specified, and any monetary figure in United States dollars shall be deemed to refer to the equivalent amount of foreign currency when used in a context which refers to or includes operations conducted principally outside of the United States;

(i) References to "include," "includes" and "including" in this Agreement shall be deemed to be followed by ", without limitation," whether or not so specified; and

(j) The word "extent" in the phrase "to the extent" shall mean the degree to which a subject or other theory extends, and such phrase shall not mean "if."

4.2. Further Actions. Each party hereto shall cooperate with each other party, shall do and perform or cause to be done and performed all further acts and things, and shall execute and deliver all other agreements, certificates, instruments and documents as any other party hereto reasonably may request in order to carry out the intent and accomplish the purposes of this Agreement and the consummation of the transactions contemplated hereby.

4.3. Notices.

(a) Unless otherwise expressly provided herein, all notices, requests, demands, claims and other communications provided for under the provisions of this Agreement shall be in writing. Any notice, request, demand, claim or other communication hereunder shall be sent by (i) personal delivery (including receipted courier service) or overnight delivery service to the intended recipient at the address set forth below, (ii) facsimile or electronic mail, with confirmation of receipt, to the number or email address of the intended recipient set forth below (provided that a copy is also sent by another permitted method; and provided, further, that delivery to the NMP Entities may not be sent by facsimile), (iii) internationally recognized overnight delivery courier service to the intended recipient at the address set forth below, or

(iv) registered or certified mail, return receipt requested, postage prepaid, to the intended recipient at the address set forth below:

(i) If to the Company, at the address indicated below, or at such other address as the Company may hereafter designate by written notice to the Holders:

Bellerophon Therapeutics, Inc.
53 Frontage Road, Suite 301
Hampton, NJ 08827
Attn: Chief Executive Officer
Fax: 844-325-6587
Email: jon.peacock@bellerophon.com

with copies (which shall not constitute notice) to:

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attn: Lia Der Marderosian, Esq.
Fax: +1-617-526-5000
Email: lia.dermarderosian@wilmerhale.com

and

Fried, Frank, Harris, Shriver & Jacobson LLP
One New York Plaza
New York, NY 10004
Attn: Aviva F. Diamant, Esq. and Abigail P. Bomba, Esq.
Fax: +1-212-859-4000
Email: aviva.diamant@friedfrank.com and
abigail.bomba@friedfrank.com

(ii) If to any Holder, to such Holder at the address set forth below such Holder's name on its signature page hereto, or at such other address as such Holder may hereafter designate by written notice to the Company, in each case, with a copy (which shall not constitute notice) to:

Fried, Frank, Harris, Shriver & Jacobson LLP
One New York Plaza
New York, NY 10004
Attn: Aviva F. Diamant, Esq. and Abigail P. Bomba, Esq.
Fax: +1-212-859-4000
Email: aviva.diamant@friedfrank.com and
abigail.bomba@friedfrank.com

and

Wilmer Cutler Pickering Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attn: Lia Der Marderosian, Esq.
Fax: +1-617-526-5000
Email: lia.dermarderosian@wilmerhale.com

(iii) If to any Tag-Along Holder, to such Tag-Along Holder at its address set forth on the books and records of the Company.

(b) Notices shall be deemed to have been received:

(i) If given by personal delivery or by facsimile or electronic transmission, on the day given, if given before 5:00 PM local time on a Business Day in the jurisdiction of the intended recipient; otherwise on the next Business Day, provided that receipt of any facsimile or electronic transmission is confirmed by written evidence of delivery of facsimile, electronic confirmation of delivery or written acknowledgment of receipt thereof by the recipient;

(ii) If given by internationally recognized overnight delivery courier service, on the date of delivery indicated in the records of such courier service; and

(iii) If given by registered or certified mail, return receipt requested, postage prepaid, on the date of delivery indicated on the return receipt.

4.4. Governing Law. This Agreement shall in all respects be governed by, and construed in accordance with, the laws (excluding conflict of laws rules and principles) of the State of Delaware applicable to agreements made and to be performed entirely within such State, including all matters of construction, validity and performance.

4.5. Specific Performance. The parties agree that irreparable damage would occur in the event that any of the provisions of this Agreement were not performed in accordance with its specific terms or were otherwise breached and that money damages or other remedy at law would not be a sufficient or adequate remedy for any breach or violation of, or a default under, this Agreement. It is accordingly agreed that, subject to Section 4.8, each of the parties shall be entitled, without any requirement for the securing or posting of any bond with respect to such remedy, to an injunction or injunctions to prevent or restrain any breach, violation or default, or threatened breach, violation or default, of this Agreement and to enforce specifically the terms and provisions hereof in any court of the United States or any state having jurisdiction, such remedy being in addition to any other remedy to which any party may be entitled at law or in equity.

4.6. Entire Agreement. This Agreement, including, to the extent referred to herein, the Pre-IPO Certificate of Incorporation, the Certificate of Incorporation and the Stockholders Agreement, constitutes the entire agreement of the parties relating to the subject matter hereof

and supersedes all prior agreements and undertakings, whether oral or written. For avoidance of doubt, this Agreement supersedes and replaces the Original Registration Rights Agreement, which agreement shall no longer have any force or effect. There are no representations, agreements, arrangements or understandings, oral or written, between or among the parties relating to the subject matter of this Agreement which are not fully expressed in this Agreement.

4.7. Severability. Should any provision of this Agreement or the application thereof to any Person or circumstance be held invalid or unenforceable to any extent, (a) such provision shall be ineffective to the extent, and only to the extent, of such invalidity or unenforceability and shall be enforced to the greatest extent permitted by law; (b) such invalidity or unenforceability with respect to any Person or in any jurisdiction shall not invalidate or render unenforceable such provision as applied (i) to any other Persons or circumstances or (ii) in any other jurisdiction; and (c) such invalidity or unenforceability shall not affect or invalidate any other provision of this Agreement.

4.8. Amendments and Waivers.

(a) Subject to Section 4.8(c), this Agreement and any of the provisions hereof may be amended, modified or supplemented, in whole or in part, only by written agreement of the Company (with the prior approval of the Board) and Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders; provided that (i) any amendment or modification of, or supplement to, Section 2.6 that relates only to a particular offering shall require only the written agreement of the Company (with the prior approval of the Board) and the Majority Participating Holders for such offering, and (ii) any amendment or modification of, or supplement to, this Agreement the direct result of which is to materially adversely affect any Holder (or class or series of Holders) in a manner that is materially different from the manner in which the other Holders (or other classes or series of Holders) are affected (other than such materially different effects resulting from the express provisions of this Agreement in effect immediately prior to such amendment, modification or supplement) may be effected only with the prior written consent of such Holder (or a majority of such class or series of Holders measured by the number of shares of the class or series held) so differently affected.

(b) The observance of any provision of this Agreement may be waived in writing by the Company (with the prior approval of the Board) and Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders; provided that any provision hereof may be waived by any waiving party on such party's own behalf, without the consent of any other party. Any waiver of any provision of Section 2.6 that relates only to a particular offering shall require only the written agreement of the Company (with the prior approval of the Board) and the Majority Participating Holders for such offering. Any waiver by any party hereto of a breach by any party hereto of any provision of this Agreement shall not operate or be construed as a waiver of such breach by any other party hereto, except as otherwise explicitly provided for in the writing evidencing such waiver. Except as otherwise expressly provided herein, no failure on the part of any party to exercise, and no delay in exercising, any right, power or remedy hereunder, or otherwise available in respect hereof at law or in equity, shall operate as a waiver thereof, nor shall any single or partial exercise of such

right, power or remedy by such party preclude any other or further exercise thereof or the exercise of any other right, power or remedy.

(c) Other than in the case of a Permitted Assignee (which shall not require the consent of the Company or any Holder), the execution of a counterpart signature page or a joinder to this Agreement after the date hereof by any Person holding any Equity Interests of the Company shall require the consent of the Company (with the prior approval of the Board) and Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders and shall not be deemed an amendment to this Agreement so long as such Person agrees to be treated as a "Holder" hereunder.

4.9. No Third Party Beneficiaries. Other than Section 2.6, nothing in this Agreement, whether express or implied, shall be construed to give any Person (other than the parties hereto and their respective successors and permitted assigns who comply with the terms hereof and agree in writing to be bound by the provisions hereof) any legal or equitable right, remedy or claim under or in respect of this Agreement or any covenants, conditions or provisions contained herein, as a third party beneficiary or otherwise. Each Indemnitee shall be a third party beneficiary of the provisions of Section 2.6 and shall be entitled to enforce such provisions directly. The Tag-Along Holders (except as set forth in the immediately preceding sentence) shall not be third party beneficiaries of this Agreement and shall not be entitled to enforce any of the provisions hereof, provided that nothing in this Agreement shall limit the rights of the Tag-Along Holders under the Pre-IPO Certificate of Incorporation.

4.10. Assignments. The provisions of this Agreement shall be binding upon and inure to the benefit of the Company and the Holders and their respective successors and permitted assigns. The Company may not assign any of its rights or delegate any of its duties hereunder without the prior written consent of Holders holding in the aggregate at least fifty percent (50%) of the outstanding Registrable Securities then held by the Holders. With respect to the Holders, (a) prior to an Initial Public Offering, any Holder may, at its election and at any time or from time to time, assign its rights and delegate its duties hereunder, in whole or in part, to any Person to whom such Holder transfers any of such Holder's Equity Interests in compliance with the Pre-IPO Certificate of Incorporation and (b) at any time or from time to time following an Initial Public Offering, (i) any Holder may transfer its rights and delegate its duties hereunder, in whole or in part, to an Affiliate of such Holder and (ii) any NMP Holder may additionally transfer its rights and delegate its duties hereunder, in whole or in part, to any Person that acquires shares of Common Stock from an NMP Holder in a transaction other than a Public Offering or a sale pursuant to Rule 144 (each of the assignees referenced in clauses (a), (b)(i) and (b)(ii) of this sentence is referred to as a "**Permitted Assignee**"), provided, that an NMP Holder may only transfer in a transaction described in clause (b)(ii) above its then remaining demand registration rights under Section 2.1 (in whole or in part) to a Person that, immediately following such transfer, will hold, together with its Affiliates, at least ten percent (10%) in the aggregate of the Quarterly Outstanding Common Stock unless such transfer is of the balance of the Registrable Securities then held by all the NMP Holders in which case an NMP Holder may only transfer in such a transaction one or more of its then remaining demand registration rights under Section 2.1 to a Person that, immediately following such transfer, will hold, together with its Affiliates, at least five percent (5%) in the aggregate of the Quarterly Outstanding Common Stock. For the

avoidance of doubt, there may be more than one transfer under any of clauses (a), (b)(i) and (b)(ii) of the preceding sentence. Notwithstanding the foregoing, no such assignment shall be binding upon or obligate the Company to any such Permitted Assignee unless and until such Permitted Assignee delivers to the Company (i) a written notice stating the name and address of such Assignee and identifying the Equity Interests of the Company with respect to which such rights are being assigned, if any, and (ii) a written instrument by which such Permitted Assignee agrees to be bound by the obligations imposed upon Holders under this Agreement to the same extent as if such Permitted Assignee were a party hereto (or executes and delivers to the Company a counterpart signature page or a joinder to this Agreement and agrees to be treated as a "Holder" for all purposes of this Agreement), whereupon such Permitted Assignee shall be entitled to all of the rights of a Holder under this Agreement, including under this Section 4.10.

4.11. Jurisdiction; Waiver of Jury Trial.

(a) Jurisdiction. Subject to Section 4.5, any action, suit or proceeding against any party to this Agreement arising out of or relating to this Agreement shall be brought in any federal or state court located in New York County in the State of New York, and each of the parties hereby submits to the exclusive jurisdiction of such courts for the purpose of any such action, suit or proceeding. A final judgment in any such action, suit or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by law. To the extent that service of process by mail or by internationally recognized overnight delivery courier service is permitted by applicable law, each party irrevocably consents to the service of process in any such action, suit or proceeding in such courts by the mailing of such process by registered or certified mail, postage prepaid, return receipt request or by internationally recognized overnight delivery courier service to such party at its address for notices provided for in Section 4.3. Each party irrevocably waives and agrees not to assert (i) any objection which it may ever have to the laying of venue of any such action, suit or proceeding in any federal or state court located in New York County in the State of New York, and (ii) any claim that any such action, suit or proceeding brought in any such court has been brought in an inconvenient forum.

(b) Waiver of Jury Trial. EACH PARTY IRREVOCABLY WAIVES, TO THE EXTENT LAWFUL, AND AGREES NOT TO ASSERT ANY RIGHT TO TRIAL BY JURY IN ANY ACTION, SUIT OR PROCEEDING ARISING OUT OF RELATING TO THIS AGREEMENT AND AGREES THAT ANY OF THEM MAY FILE A COPY OF THIS PARAGRAPH WITH ANY COURT AS WRITTEN EVIDENCE OF THE KNOWING, VOLUNTARY AND BARGAINED-FOR AGREEMENT AMONG THE PARTIES IRREVOCABLY TO WAIVE ITS RIGHT TO TRIAL BY JURY IN ANY ACTION, SUIT OR PROCEEDING ARISING OUT OF RELATING TO THIS AGREEMENT.

4.12. Attorneys' Fees. In the event that any action, suit or proceeding is brought for the purpose of determining or enforcing the right of any party or parties hereunder, the party or parties prevailing in such action, suit or proceeding shall be entitled to recover from the other party or parties all reasonable costs and expenses incurred by the prevailing party or parties in connection with such action, suit or proceeding, including reasonable attorneys' fees.

4.13. Counterparts. This Agreement may be executed in any number of counterparts with the same effect as if all signatory parties had signed the same document. All counterparts shall be construed together and shall constitute one and the same instrument. A signature delivered by facsimile or electronic transmission shall be deemed to be an original signature for all purposes under this Agreement.

4.14. Effectiveness. Except for (a) Indemnitees and (b) as otherwise provided in the Pre-IPO Certificate of Incorporation and in this Agreement with respect to Tag-Along Securities, no Person shall have any rights under this Agreement, and neither the Company nor any Holder shall have any obligations under this Agreement to any other Person, unless and until such other Person has executed and delivered this Agreement or a counterpart hereto agreeing to be bound by this Agreement as a Holder. The failure of any one or more Persons to execute and deliver this Agreement or a counterpart hereto shall not invalidate this Agreement or any of the rights and obligations of the Company and of those Holders that have executed and delivered this Agreement or a counterpart hereto as among such parties that have so executed and delivered this Agreement or a counterpart hereto.

[*Signature Page Follows*]

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

COMPANY:

BELLEROPHON THERAPEUTICS, INC.

By: /s/ Jonathan M. Peacock
Name: Jonathan M. Peacock
Title: President and Chief Executive Officer

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

HOLDERS:

NEW MOUNTAIN PARTNERS II (AIV-A), L.P.

By: New Mountain Investments II, L.L.C.,
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

NEW MOUNTAIN PARTNERS II (AIV-B), L.P.

By: New Mountain Investments II, L.L.C.,
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

NEW MOUNTAIN AFFILIATED INVESTORS II, L.P.

By: New Mountain Investments II, L.L.C.,
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

ALLEGHENY NEW MOUNTAIN PARTNERS, L.P.

By: New Mountain Investments II, L.L.C.,
Its general partner

By: /s/ Steven B. Klinsky
Name: Steven B. Klinsky
Title: Managing Member

Address for notices:

c/o New Mountain Capital, L.L.C.
787 Seventh Avenue, 49th Floor
New York, NY 10019
Attn: Matthew Holt
Email: mholt@newmountaincapital.com

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

HOLDER:

ARCH VENTURE FUND VI, L.P.

By: ARCH Venture Partners VI, L.P.,
Its general partner

By: ARCH Venture Partners VI, LLC,
Its general partner

By: /s/ Robert T. Nelsen
Name: Robert T. Nelsen
Title: Managing Director

Address for notices:

c/o ARCH Venture Partners
8725 West Higgins Road
Suite 290
Chicago, IL 60631
Attn: Mark McDonnell
Fax: +1-773-380-6606
Email: mmcdonnell@archventure.com

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

HOLDERS:

VENROCK PARTNERS, L.P.

By: Venrock Partners Management, LLC,
Its general partner

By: /s/ Bryan E. Roberts
Name: Bryan E. Roberts
Title: General Partner

VENROCK ASSOCIATES IV, L.P.

By: Venrock Management IV, LLC,
Its general partner

By: /s/ Bryan E. Roberts
Name: Bryan E. Roberts
Title: General Partner

VENROCK ENTREPRENEURS FUND IV, L.P.

By: VEF Management IV, LLC,
Its general partner

By: /s/ Bryan E. Roberts
Name: Bryan E. Roberts
Title: General Partner

Address for notices:

c/o Venrock Associates
3340 Hillview Avenue
Palo Alto, CA 94304
Attn: Bryan Roberts
Fax: +1-650-561-9180
Email: broberts@venrock.com

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

HOLDER:

LINDE NORTH AMERICA, INC.

By: /s/ Jens Luehring
Name: Jens Luehring
Title: Head of Finance, Americas

Address for notices:

Linde North America, Inc.
575 Mountain Avenue
Murray Hill, NJ 07974
Fax: +1.908.771.1852

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

HOLDERS:

5AM VENTURES LLC

By: 5AM Partners LLC,
Its manager

By: /s/ Andrew J. Schwab
Name: Andrew J. Schwab
Title: Managing Director

5AM CO-INVESTORS LLC

By: 5AM Partners LLC,
Its manager

By: /s/ Andrew J. Schwab
Name: Andrew J. Schwab
Title: Managing Director

Address for notices:

c/o 5AM Ventures LLC
2200 Sand Hill Road, Suite 110
Menlo Park, CA 94025
Attn: Andrew Schwab
Fax: +1-650-233-8923
Email: andy@5amventures.com

IN WITNESS WHEREOF, the parties hereto have executed and delivered this Agreement as of the date first above written.

HOLDER:

ARAVIS VENTURE I, L.P.

By: Aravis General Partner Ltd,
Its general partner

By: /s/ Jean-Philippe Tripet
Name: Jean-Philippe Tripet
Title: Chairman

Address for notices:

c/o Aravis General Partner Ltd
One Capital Place
P.O. Box 847
Grand Cayman KY1-1103
Cayman Islands
Attn: Gwen McLaughlin

With a copy by email to:

Email: andreas@aravis.ch

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

The Board of Directors
Bellerophon Therapeutics, Inc.:

We consent to the incorporation by reference in the registration statement (No. 333-202069) on Form S-8 of Bellerophon Therapeutics, Inc. of our report dated March 31, 2015, with respect to the consolidated balance sheets of Bellerophon Therapeutics LLC as of December 31, 2014 and 2013, and the related consolidated statements of operations and comprehensive loss, changes in members' equity and invested equity (deficit), and cash flows for each of the years in the three-year period ended December 31, 2014, which report appears in the December 31, 2014 annual report on Form 10-K of Bellerophon Therapeutics, Inc.

/s/ KPMG LLP

Short Hills, New Jersey
March 31, 2015

Exhibit 31.1

CERTIFICATION

I, Jonathan M. Peacock, certify that:

1. I have reviewed this Annual Report on Form 10-K of Bellerophon Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 31, 2015

By: /s/ Jonathan M. Peacock
Jonathan M. Peacock
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION

I, David Abrams, certify that:

1. I have reviewed this Annual Report on Form 10-K of Bellerophon Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 31, 2015

By: /s/ David Abrams
David Abrams
Treasurer
(Principal Financial Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Bellerophon Therapeutics, Inc. (the "Company") for the year ended December 31, 2014 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Jonathan M. Peacock, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 31, 2015

By: /s/ Jonathan M. Peacock
Jonathan M. Peacock
Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Bellerophon Therapeutics, Inc. (the "Company") for the year ended December 31, 2014 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, David Abrams, Treasurer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that to his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 31, 2015

By: /s/ David Abrams
David Abrams
Treasurer
(Principal Financial Officer)