UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

FORM 10-K

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

For the fiscal year ended December 31, 2018

☐ **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 001-38137

Akcea Therapeutics, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**47-2608175**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)
22 Boston Wharf Road, 9th Floor, Boston, MA	**02110**
(Address of Principal Executive Offices)	(Zip Code)

617-207-0202
(Registrant's telephone number, including area code)

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

Title of each class	Name of each exchange on which registered
Common Stock, $.001 Par Value	The Nasdaq Stock Market, LLC

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 every Interactive Data File required to be submitted 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 such files). Yes ☒ No☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K 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, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act:

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Smaller reporting company	☐
Emerging growth company	☒		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

The aggregate market value of the common stock held by non-affiliates of the registrant was approximately $209.3 million as of June 30, 2018 based upon the closing sale price on the NASDAQ Global Select Market reported for such date. Shares of common stock held by each executive officer and director and certain holders of more than 10% of the outstanding shares of the registrant's common stock have been excluded in that such persons may be deemed to be affiliates. Shares of common stock held by other persons, including certain other holders of more than 10% of the outstanding shares of common stock, have not been excluded in that such persons are not deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares of common stock outstanding as of February 20, 2019 was 89,433,187.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Information Statement with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders are incorporated by reference into Part III of this Report. Such information statement will be filed with the Securities and Exchange Commission not later than 120 days following the end of the Registrant's fiscal year ended December 31, 2018.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly risks related to our financial condition and need for additional capital, the clinical development and regulatory review and approval of our drugs, the commercialization of our drugs, our dependence on third parties to develop and commercialize our drugs, our relationship with Ionis Pharmaceuticals, Inc., our controlling stockholder, and risks related to our business and industry generally, such as risks inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These statements, like all statements in this report, speak only as of the date of this annual report on Form 10-K (unless another date is indicated), and we undertake no obligation to update or revise these statements in light of future developments.

In this report, unless the context requires otherwise, "Akcea," "Company," "we," "our," and "us" refers to Akcea Therapeutics, Inc. and its subsidiaries.

TRADEMARKS

"Akcea," the Akcea logo, TEGSEDI, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in this report are the property of Akcea Therapeutics, Inc. This report contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this report may appear without the ® or TM symbols.

AKCEA THERAPEUTICS, INC.
ANNUAL REPORT ON FORM 10-K FOR THE YEAR ENDED DECEMBER 31, 2018
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PART I

Item 1. Business

Overview

We are a commercial stage biopharmaceutical company developing and marketing drugs globally to treat patients with rare and serious diseases. We are bringing novel and transformative medicines to patients by driving clinical program execution, understanding patient and physician needs, preparing the market, creating market access, and commercializing our products on a global basis. As an affiliate of Ionis Pharmaceuticals, Inc., or Ionis, we have a robust portfolio of development-, registration- and commercial-stage drugs covering multiple targets and diseases using antisense therapeutics. Our immediate focus is on the commercial launch of our first commercially approved therapy, TEGSEDI in the United States, or U.S., the European Union, or E.U., and Canada. TEGSEDI treats the polyneuropathy caused by hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults. We estimate that there are approximately 50,000 patients globally with hATTR amyloidosis, the majority of whom have symptoms of polyneuropathy. We are also focused on commercial preparations for WAYLIVRA in the E.U. and on regulatory discussions for WAYLIVRA in the U.S. and Canada. The Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, we plan to leverage our existing commercial infrastructure in Europe to market WAYLIVRA. FCS is an ultra-rare, devastating hereditary disease that causes unpredictable and potentially fatal acute pancreatitis, chronic complications due to permanent organ damage, and a severe impact on daily living. The hallmark of FCS is extremely elevated triglycerides. There are approximately 3,000 to 5,000 patients with FCS worldwide. We are advancing a mature pipeline of novel drugs with the potential to treat multiple diseases. TEGSEDI, WAYLIVRA and our pipeline drugs, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}, are all based on Ionis' antisense technology platform. Our pipeline drugs use Ionis' advanced Ligand Conjugated Antisense, or LICA, technology, which enhances the effective uptake and activity of these drugs in particular tissues.

TEGSEDI is the world's first subcutaneous, RNA-targeted therapeutic that substantially reduces the production of transthyretin, or TTR protein. Importantly, TEGSEDI is Akcea's first commercially approved drug, and our launch is underway in three regions: the U.S., the E.U. and Canada. We continue to work toward our goal to make TEGSEDI available to people globally.

We are continuing to build our commercial infrastructure to support TEGSEDI, and plan to use this infrastructure to support WAYLIVRA and the other drugs in our pipeline, if approved in the future as we anticipate further commercialization in serious and rare diseases. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed rare and serious diseases will allow us to partner efficiently and effectively with the specialized medical community that supports these underserved patient communities. For example, at approval we launched Akcea Connect™, a drug treatment program made up of dedicated, regionally-based nurse case managers who have a wide range of medical knowledge and experience, in the United States. This program offers free, private and personalized support to patients and their caregivers and families across the country. Internationally, Akcea Connect is being rolled out in each of the countries where we launch with what we believe is the highest level of patient and physician support allowed in accordance with local regulations. In addition, in August 2018 we entered into an agreement with Express Scripts' Accredo to be our specialty pharmacy partner for the distribution of TEGSEDI in the U.S. We chose Express Scripts' Accredo Health Group, Inc., or Accredo because of their experience supporting the unique needs of rare disease communities and their proven track record for simplifying access to therapy. Accredo has a team of specialty clinicians, pharmacists and over 600 field-based nurses located throughout the U.S. who are augmenting the Akcea Connect team of nurse case managers to provide support and address the needs of the hATTR amyloidosis community. Our supply chain is fully operational in the U.S., E.U. and Canada. To further support the hATTR amyloidosis community, Akcea and Ambry Genetics Corporation, or Ambry, a Konica Minolta company, launched hATTR Compass™ in the U.S. and Canada, a no-cost, confidential genetic testing and genetic counseling program for people with suspected hATTR amyloidosis. This program is intended to empower people with accurate genetic information, so they can make informed decisions about their healthcare.

As we build Akcea, we continue to execute a strategy for expansion of our business globally. Depending on the geographic region, the number of patients impacted by the diseases we are treating and the regulatory environment of the local countries, in some regions we may choose to build out the commercial infrastructure ourselves, and in other instances, we may choose to partner with another company for commercial sales and distribution. For instance, in August 2018, we entered into a licensing agreement with PTC Therapeutics International Limited, or PTC Therapeutics, to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Our decision to partner with PTC to accelerate commercial access for patients in Latin America reflects our commitment to bringing TEGSEDI and WAYLIVRA to patients as rapidly as possible. PTC has an established rare disease team in Latin America that has experience in patient identification, in physician and patient education and support programs and in efficiently obtaining market access. PTC's patient-focused approach for rare diseases aligns with our approach, making them a great partner for this region.

To maximize the commercial potential of two of the drugs in our pipeline, we initiated a strategic collaboration with Novartis Pharma AG, or Novartis, for the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx}. Novartis is currently preparing to initiate a Phase 3 study of AKCEA-APO(a)-L_{Rx} in patients with established cardiovascular disease (CVD) and elevated levels of lipoprotein(a), or Lp(a). We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. As part of our collaboration, we received $75.0 million in an upfront option payment, of which we retained $60.0 million and paid $15.0 million to Ionis as a sublicense fee. We also earned a $150.0 million license fee when Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} of which we will pay $75.0 million to Ionis as a sublicense fee. We will pay Ionis the sublicense fee in Akcea common stock. Novartis is now responsible for all future development and commercialization activities for AKCEA-APO(a)-L_{Rx}. We are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APO(a)-L_{Rx} from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. In connection with Novartis' exercise of its option to exclusively license AKCEA-APO(a)-L_{Rx}, Akcea and Novartis established a more definitive framework under which they would negotiate the co-commercialization of AKCEA-APO(a)-L_{Rx} between the two companies in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L_{Rx} in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L_{Rx}. We will share any license fees, milestone payments and royalties equally with Ionis.

For AKCEA-APOCIII-L_{Rx}, under our agreement with Novartis, after we complete Phase 2 development and if Novartis exercises its option to license AKCEA-APOCIII-$L_{Rx,}$ we would receive an additional $150.0 million license fee which we would also share equally with Ionis. If exercised, Novartis would conduct and pay for a Phase 3 cardiovascular outcome study in patients with hypertriglyceridemia and prior cardiovascular risk. If approved, Novartis would commercialize AKCEA-APOCIII-L_{Rx} worldwide. Novartis will have 60 days plus additional time that could be required for Hart-Scott-Rodino, or HSR, filing and review following the end-of-Phase 2 meeting to exercise its option for AKCEA-APOCIII-L_{Rx}. As part of the collaboration, we may co-commercialize AKCEA-APOCIII-L_{Rx} in selected markets, on mutually agreed terms and conditions. Similar to AKCEA-APO(a)-L_{Rx}, we are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APOCIII-L_{Rx} from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. We will share any license fees, milestone payments and royalties equally with Ionis.

Our Strategy

We believe we are on our way to becoming a premier global biotechnology company offering treatments for previously inadequately treated serious and rare diseases. The critical components of our business strategy to achieve this goal include the following:

- ***Successfully commercialize TEGSEDI in multiple geographies and WAYLIVRA in the E.U.:*** We are currently marketing TEGSEDI in the U.S., E.U. and Canada. In addition, we are preparing to market WAYLIVRA in the E.U. pending the EC's adoption of the positive CHMP opinion. We have built a commercial organization in multiple countries and will continue to assess opportunities to grow in other markets as well. We are providing high touch patient and healthcare provider support through Akcea Connect. This team of dedicated nurse case managers provide reimbursement assistance, injection training and support for routine platelet monitoring, which we believe enables strong integration with treating physicians and should facilitate patient uptake and compliance. We also have partnered with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America (LATAM) and certain countries in the Caribbean. We believe our collaboration with PTC is the best way to provide these drugs to patients quickly in these markets. We also believe PTC shares the same patient-focus that we do and will be able to provide the same patient services as appropriate in each of the LATAM countries. Now that TEGSEDI is approved, our aim is to make it available globally and we will continue to assess expanding our own global footprint as well as additional strategic partnerships as we continue to commercialize TEGSEDI.

- ***Advance multiple novel clinical-stage drugs to commercialization and further grow our pipeline***. We seek to maximize near-term and long-term commercial opportunities through development paths in both orphan and broader patient populations. Our pipeline of antisense drugs currently contains five clinical-stage novel therapies that we plan to develop and commercialize by ourselves or in conjunction with a partner for multiple indications. To sustain our goal of being the premier rare and serious disease company, we also plan to actively replenish our pipeline as our current drugs advance through development. For example, we will have the opportunity to potentially license antisense drugs that Ionis advances to treat rare cardiometabolic and rare inherited metabolic diseases under our right of first negotiation that Ionis granted us. In addition to antisense technology, we are open to other technologies and products where we could potentially leverage our commercial and development expertise in rare diseases.
- ***Create value through strategic collaborations, to drive drugs to their fullest potential.*** We believe that some of our drugs could address diseases with very large patient populations. In these patient populations, large, costly, late-stage clinical development programs, as well as large sales forces, are required to maximize a drug's commercial potential. As a result, in some cases, partnering with a large organization with global scale may be the optimal approach for maximizing the potential of drugs in these indications. As an example, we have a strategic collaboration with Novartis for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-$L_{Rx.}$ Novartis recently exercised its option to license AKCEA-APO(a)-L_{Rx} and as a result they are responsible for all future clinical development and commercial activities and costs. Novartis is currently planning for a Phase 3 cardiovascular outcomes study for AKCEA-APO(a)-L_{Rx} and initiation activities are underway. If they exercise their right to license AKCEA-APOCIII-L_{Rx} they could also provide us with an opportunity to move rapidly to Phase 3 cardiovascular outcome studies, enhancing the commercial potential of that drug as well. We also may co-commercialize these two drugs in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future. We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders.

MARKETED THERAPY

TEGSEDI

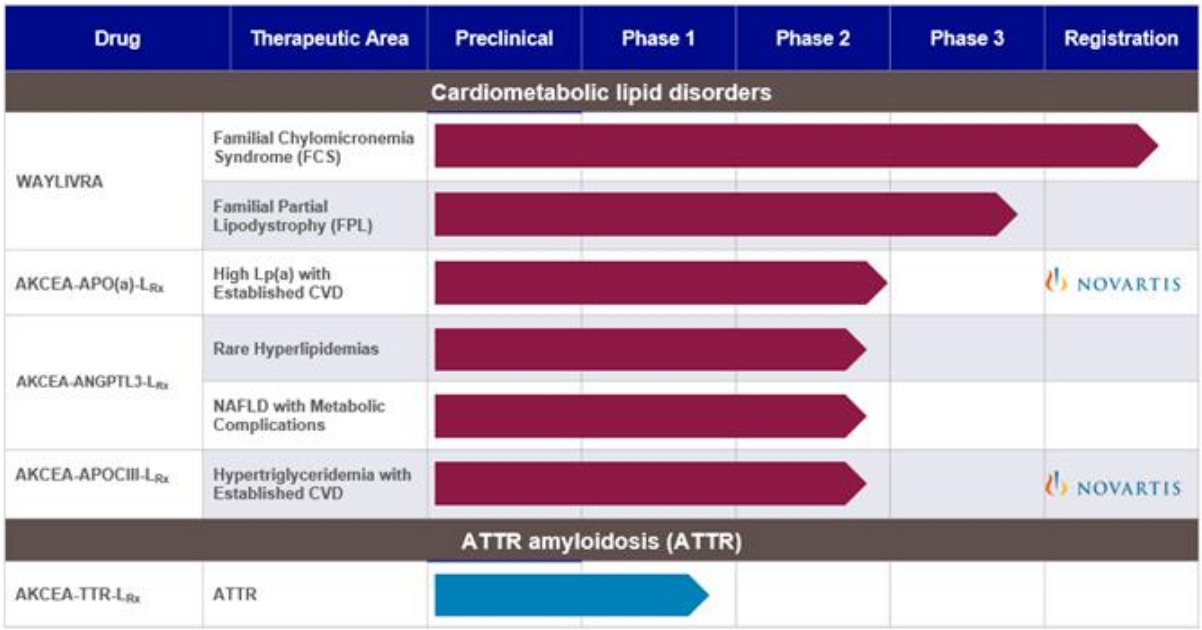
TEGSEDI is a drug that Ionis discovered and developed using Ionis' proprietary antisense technology platform. TEGSEDI is designed to reduce the production of transthyretin, or TTR, protein. In patients with hereditary transthyretin, or hATTR, amyloidosis, a severe, rare and fatal genetic disease, both the hereditary and wild-type, or wt, TTR protein builds up as fibrils in tissues, such as the peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to sensory, motor and autonomic dysfunction often having debilitating effects on multiple aspects of a patient's life and eventually leads to death.

TEGSEDI is now approved in three markets: the U.S., E.U. and Canada. On October 5, 2018, we received approval from the U.S. Food and Drug Administration, or FDA, for TEGSEDI for the treatment of the polyneuropathy of hATTR amyloidosis in adults. On October 3, 2018, TEGSEDI was approved by Health Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. And on July 11, 2018, TEGSEDI received marketing authorization, or MA, approval from the European Commission, or EC, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR amyloidosis. We estimate that there are approximately 50,000 patients globally with hATTR amyloidosis, the majority of whom have symptoms of polyneuropathy. TEGSEDI is available in the U.S., Germany and Canada and we continue to work today on making TEGSEDI available to patients across various European countries with the ultimate goal of making TEGSEDI available to patients globally.

Disease Background

hATTR amyloidosis is a rare, progressive, and fatal disease that often affects multiple organs, including the nerves, heart, gastrointestinal tract and kidneys. hATTR amyloidosis occurs when misfolded TTR protein deposits throughout the body as amyloid fibrils, disrupting tissue and organ structure and function. The burden of hATTR amyloidosis is high as patients often suffer from progressive neuropathy, cardiac, gastrointestinal and psychosocial symptoms affecting every aspect of their life. Without therapeutic intervention, patient quality of life progressively and rapidly deteriorates, leading to a reduction in ambulation and daily function, and ultimately resulting in premature death. As the disease progresses, many patients are no longer able to work and or are forced to take substantial time off. The impact of the disease is not limited to physical symptoms but also impacts mental health and outlook as patients often live in fear and isolation. An accurate and timely diagnosis and early treatment initiation is critical to optimize disease management.

PIPELINE



All products were discovered by Ionis and either developed by Ionis or co-developed by Ionis and Akcea.

WAYLIVRA

WAYLIVRA was discovered by Ionis and is being co-developed by Akcea and Ionis and is based on Ionis' antisense technology platform. WAYLIVRA is designed to address the serious and unmet medical needs of the underserved FCS patient community. We are focused on commercial preparations for WAYLIVRA in the E.U. and on regulatory discussions for WAYLIVRA in the U.S. and Canada. The CHMP of the EMA has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, we plan to leverage our existing commercial infrastructure in Europe to market WAYLIVRA. In the U.S., on May 10, 2018, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted to support approval of WAYLIVRA for the treatment of people with FCS. On August 27, 2018, we and Ionis announced that we received a Complete Response Letter from the Division of Metabolism and Endocrinology Products of the FDA regarding the New Drug Application for WAYLIVRA. The FDA did not cite any new concerns beyond those described in the advisory committee briefing book, in which the main areas of focus were the dosing schedule and management of thrombocytopenia, a deficiency of platelets in the blood. In November 2018, we received a Notice of Noncompliance withdrawal letter, or NON-W, from Health Canada for WAYLIVRA. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA.

FCS is a severe and rare lipid disorder characterized by extremely elevated levels of triglycerides. FCS has life-threatening consequences such as acute pancreatitis and the lives of patients with this disease are impacted daily by the associated symptoms. In our clinical program, we have observed consistent and substantial (>70%) decreases in triglycerides and improvements in other manifestations of FCS, including pancreatitis attacks and abdominal pain. We believe the safety and efficacy data from the WAYLIVRA program demonstrate a favorable risk-benefit profile for patients with FCS. The FDA and EMA have granted orphan drug designation to WAYLIVRA for the treatment of patients with FCS.

WAYLIVRA is also in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. People with FPL lack subcutaneous adipose tissue and have abnormal subcutaneous fat distribution causing increased incidence of potentially life-threatening pancreatitis, diabetes, extreme insulin resistance and increased liver fat. BROADEN is a randomized, double-blind, placebo-controlled study of 300 mg of WAYLIVRA administered by a subcutaneous injection in patients with FPL. We plan to report results from the BROADEN study this year.

LICA Pipeline

The other drugs in our pipeline - AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx} utilize Ionis' advanced Ligand Conjugated Antisense, or LICA, technology. LICA technology conjugates specific chemical structures or molecules to antisense drugs to increase the efficiency of drug uptake in a particular tissue. We believe the enhancements from LICA technology have the potential to allow for less frequent administration and significantly lower doses, providing greater patient convenience. Data from a number of Phase 1 studies and our Phase 2 study of AKCEA-APO(a)-L_{Rx} have shown that doses up to 30-fold lower than non-LICA drugs result in consistent target reductions and a favorable safety and tolerability profile. Our current pipeline includes drugs with the potential to treat patients with ATTR and a wide range of lipid disorders associated with cardiometabolic disease that other technologies, such as small molecules and antibodies, have not been able to adequately address.

Our clinical pipeline contains novel drugs with the potential to treat inadequately addressed serious and rare disorders.

AKCEA-APO(a)-L$_{Rx}$. We are developing AKCEA-APO(a)-L_{Rx} for patients who are at significant risk of cardiovascular disease, or CVD, because of their elevated levels of Lp(a). AKCEA-APO(a)-L_{Rx} inhibits the production of the apolipoprotein(a), or apo(a), protein, thereby reducing Lp(a). Apo(a) is a form of low-density lipoprotein, or LDL, that is very atherogenic (promoting the formation of plaques in the arteries) and very thrombogenic (promoting the formation of blood clots). In September 2018, we reported positive results from the Phase 2 dose-ranging study of AKCEA-APO(a)-L_{Rx} in patients with elevated levels of Lp(a) greater than 60 mg/dL, and established CVD.

In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx}. Planning and initiation activities are underway for Novartis to run a Phase 3 cardiovascular outcomes study of AKCEA-APO(a)-L_{Rx} in patients with established CVD and elevated levels of lipoprotein(a), or Lp(a). We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver this potential therapy to patients at risk of CVD due to elevated levels of Lp(a). If AKCEA-APO(a)-L_{Rx} is approved, Novartis will be responsible for worldwide commercialization. As part of the collaboration, we may co-commercialize AKCEA-APO(a)-L_{Rx} in selected markets, on mutually agreed terms and conditions.

Novartis' decision follows positive results from a Phase 2 study in this patient population. The Phase 2 study was designed to evaluate the safety and tolerability of AKCEA-APO(a)-L_{Rx} and to determine the appropriate dosing for a planned Phase 3 cardiovascular outcomes study. The randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study included 286 patients with established CVD and high Lp(a) levels (baseline mean of approximately 100mg/dL [250 nmol/L] - more than three times the upper limit of normal). The trial had five cohorts: 20 mg (every 4 weeks), 40 mg (every 4 weeks), 60 (every 4 weeks), 20 mg (every 2 weeks), and 20 mg (every week). The primary efficacy endpoint was the percent change in Lp(a) from baseline at the primary analysis time point (6 months) compared to placebo. The secondary efficacy endpoints were mean percent change in LDL-C, apoB, OxPL-apoB, OxPL-apo(a), and the number of patients reaching pre-specific thresholds of Lp(a) reduction of <125 nmol/L (<50 mg/dL) or <75 nmol/L (<30 mg/dL). Patients were treated with AKCEA-APO(a)-L_{Rx} or placebo for at least six months, with some patients treated up to one year. The study met all primary and secondary efficacy endpoints analyzed at 6 months. Results from the study show statistically significant and dose dependent reductions from baseline in Lp(a) levels:

Lp(a)	**Pooled placebo (n=47)**	**20 mg every 4 weeks (n=48)**	**40 mg every 4 weeks (n=48)**	**20 mg every 2 weeks (n=48)**	**60 mg every 4 weeks (n=47)**	**20 mg weekly (n=48)**
LSMean % change in Lp(a)	-6	-35 P=0.0032	-56 P<0.0001	-58 P<0.0001	-72 P<0.0001	-80 P<0.0001

*LSMean: Least squares mean

- Approximately 98% of patients in the 20mg weekly cohort and approximately 81% of patients in the 60mg every 4 week cohort achieved clinically significant reductions in Lp(a) levels bringing them below the recommended threshold of risk for CVD events (<50 mg/dL).
- Treatment with AKCEA-APO(a)-L_{Rx} was associated with decreases in LDL-C, apoB, OxPL-apoB, OxPL-apo(a).
- Most adverse events were mild. The most frequent adverse events were injection site reactions, or ISRs. ISRs occurred in 26% of patients and were mostly mild and one patient discontinued due to an ISR.
- There were no safety concerns related to platelet counts, liver function or renal function.
- No patient in the study experienced a confirmed platelet count below 100,000/mm3. The incidence of platelet levels below normal (140,000/mm^3) was comparable between the active (10.5%) and placebo (14.9%) groups.

Approximately 90% of patients completed treatment and the rate of discontinuation was comparable between the active (12.1%) and placebo (14.9%) groups.

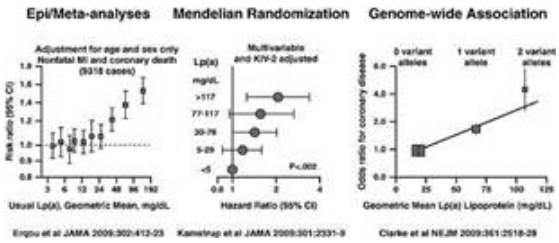
Disease Background

Despite the management of LDL-C with statins and other therapies, the incidence of CVD continues to rise dramatically. Lipid disorders are a cause of this continuing rise. Hyperlipoproteinemia(a), defined as levels of Lp(a) above 30mg/dL, which is present in approximately 20% of the general population, causes CVD.

Currently, there is no effective drug therapy to specifically and robustly lower elevated levels of Lp(a). Lp(a) levels are determined at birth and, therefore, lifestyle modification, including diet and exercise, do not impact Lp(a) levels. Statins do not have significant effects on Lp(a) levels. Further, a new class of drugs that lower LDL-C and modestly lower Lp(a) levels, known as PCSK9 inhibitors, inactivate a protein in the plasma that regulates the number of LDL receptors on the liver cell surface, thereby capturing and removing additional LDL particles from the blood. While PCSK9 inhibitors reduce Lp(a) by approximately 25%, we believe this level of reduction is unlikely to materially reduce the risk of cardiovascular events related to hyperlipoproteinemia(a). The only currently known effective way to significantly reduce plasma Lp(a) is to physically remove the particles from blood through a process called apheresis. In this process, the patient's blood is filtered through a machine where the LDL-C and Lp(a) particles are removed and the blood is returned to the patient's body. Since 2010, apheresis has been an approved therapy in Germany to treat patients with hyperlipoproteinemia(a), but it is expensive, time consuming and only performed by a small number of centers worldwide. Lp(a) apheresis has been shown to lower the rate of cardiovascular events, providing support that lowering Lp(a) can provide therapeutic benefit.

A number of expert groups, including the National Institutes for Health, European Society of Cardiology and the National Lipid Association, and publications have stated that Lp(a) is an independent cause of cardiovascular risk. The authors of three such publications evaluated data from over 180,000 participants and used statistical and genetic approaches to evaluate the correlation between Lp(a) levels and cardiovascular risk. The specific techniques the authors used were epidemiological/meta-analyses, Mendelian randomization and genome wide associations. In each technique used, the authors demonstrated a clear relationship between elevated levels of Lp(a) and increased cardiovascular risk.

The graphics below further illustrate these correlations:



AKCEA-APO(a)-L_{Rx} Commercial Opportunity

Elevated levels of Lp(a) are associated with increased cardiovascular risk and lowering Lp(a) may reduce the risk. We estimate eligible population, patients with elevated levels of Lp(a) and prior CVD, to be greater than 8 million people globally. We believe that positive results from a large cardiovascular outcome study will be required to support marketing authorization for the treatment of these patients. Since Novartis has licensed AKCEA-APO(a)-L_{Rx}, it will conduct, at its expense, such a study pursuant to our strategic collaboration and, if approved, will commercialize AKCEA-APO(a)-L_{Rx} for these patients. As part of the collaboration, we may co-commercialize AKCEA-APO(a)-L_{Rx} in selected markets, on mutually agreed terms and conditions.

- *AKCEA-ANGPTL3-L_{Rx}*. We are developing AKCEA-ANGPTL3-L_{Rx} to treat nonalcoholic fatty liver disease, or NAFLD. In preclinical studies, an analog of AKCEA-ANGPTL3-L_{Rx} inhibited the production of the angiopoietin-like 3, or ANGPTL3, protein in the liver, inhibiting liver fat accumulation and lowering blood levels of triglycerides, LDL-C and very-low-density lipoprotein cholesterol, or VLDL-C. We have completed a Phase 1/2 program for AKCEA-ANGPTL3-L_{Rx} in people with elevated triglycerides. We observed that the people with elevated triglycerides treated with AKCEA-ANGPTL3-L_{Rx} achieved dose-dependent, statistically significant mean reductions in ANGPTL3 of up to 83%. Treatment with AKCEA-ANGPTL3-L_{Rx} was also associated with statistically significant mean reductions in triglycerides of up to 66%, in LDL-C of up to 35% and in total cholesterol of up to 36%. In this study, AKCEA-ANGPTL3-L_{Rx} showed a safety and tolerability profile supporting further development. The most common adverse events in the AKCEA-ANGPTL3-L_{Rx} treated group of patients were mild headaches and dizziness that were approximately equal to the rate observed in the placebo group. We reported results for the initial cohort from this study at the AHA meeting in November 2016 and published the data in the New England Journal of Medicine. We initiated a study of AKCEA-ANGPTL3-L_{Rx} in patients with NAFLD with metabolic complications that include hypertriglyceridemia, type 2 diabetes or nonalcoholic steatohepatitis, or NASH. We expect data from this study in 2020. Further, we have a small ongoing pilot study of AKCEA-ANGPTL3-L_{Rx} in patients with rare hyperlipidemias.

Disease Background

Fatty liver disease

While some fat in the liver is normal, a significant percentage of individuals have elevated levels of liver fat. Individuals with excessive fat accumulation in the liver also have elevated risk of developing insulin resistance and metabolic syndrome, type 2 diabetes and CVD. These risks are further elevated in patients with hyperlipidemia, especially those with elevated triglyceride levels. The most common form of fatty liver disease is NAFLD, which is associated with obesity-related disorders even in patients who drink little or no alcohol, and is characterized by the gradual accumulation of fat in the liver, or steatosis. One of the key causes of this condition is the Western diet, which is rich in processed foods with high fat and sugar content. In the early stages of NAFLD, patients typically experience steatosis that is slow progressing. Over time, a subset of these patients progresses to steatohepatitis, a more severe and progressive form of NAFLD characterized by chronic inflammation and liver-cell damage, called NASH. Eventually, the chronic inflammation caused by NASH can lead to the formation of scar tissue in the liver, known as fibrosis. As scar tissue gradually replaces healthy liver tissue, blood flow is restricted, which can lead to the loss of normal liver function, cirrhosis, portal hypertension, liver cancer and ultimately liver failure. Currently, there are no approved treatments specifically for NAFLD or NASH. If the disease ultimately progresses beyond NASH, the only alternative is a liver transplant.

AKCEA-ANGPTL3-L_{Rx} Commercial Opportunity

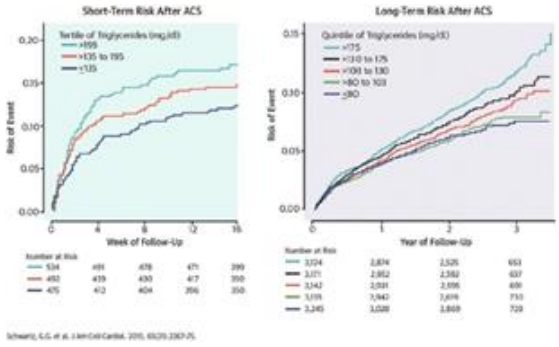
NAFLD is the most common chronic liver disease worldwide and more than 75 million patients are affected in the United States alone. Approximately 30% of patients with NAFLD will eventually progress to NASH. In the United States, the most recent epidemiological studies show that approximately 3% to 5% of the general population has NASH. We believe there are a comparable number of patients in Europe and the rest of the world. While there are a number of treatments currently in development for the treatment of NAFLD and NASH, none are currently approved and we believe there will continue to be a significant unmet medical need in this population.

- *AKCEA-APOCIII-L_{Rx}*. We are developing AKCEA-APOCIII-L_{Rx} to inhibit the production of apoC-III, the same protein inhibited by WAYLIVRA, for the broad population of patients who have cardiometabolic disease due to their elevated triglyceride levels. We believe that the enhancements offered by Ionis' LICA technology can provide greater patient convenience by allowing for significantly lower doses, less frequent administration and a favorable safety and tolerability profile. We conducted a Phase 1/2 study of AKCEA-APOCIII-L_{Rx} in people with elevated triglycerides and reported positive results from this study in the second half of 2017 with a safety and tolerability profile supporting

further development. We have initiated a strategic collaboration with Novartis for this drug. In this collaboration, we intend to complete the Phase 2 program required to define the appropriate dose and regimen to support a planned cardiovascular outcome study. We recently initiated a Phase 2b dose-ranging study of AKCEA-APOCIII-L $_{Rx}$ in patients with hypertriglyceridemia and established CVD and plan to report data from this study in 2020. At the completion of Phase 2 development, Novartis has an option to license the drug. Novartis will have 60 days plus additional time that could be required for a Hart-Scott-Rodino, or HSR, filing and review following the end-of-Phase 2 meeting to exercise its option for AKCEA-APOCIII-L_{Rx}. If Novartis exercises its option to license AKCEA-APOCIII-L_{Rx}, Novartis plans to conduct and pay for a Phase 3 cardiovascular outcome study in high-risk patients and, if approved, to commercialize AKCEA-APOCIII-L $_{Rx}$ worldwide. As part of the collaboration, we may co-commercialize AKCEA- APOCIII-L_{Rx} in selected markets, on mutually agreed terms and conditions.

Disease Background

ApoC-III is an important emerging target linking hypertriglyceridemia with CVD. Several studies have found that apoC-III levels are an independent risk factor for CVD. Further, its presence on lipoproteins may increase their atherogenicity. A study in the *New England Journal of Medicine* reported that out of a sample of over 100,000 people, individuals with an apoC-III gene loss of function mutation had a reduced risk of clinical coronary heart disease. Each decrease of 1 mg/dL in plasma levels of apoC-III was associated with a 4% decrease in the risk of incident coronary heart disease. Triglycerides may also play a role in cardiovascular risk. As shown in the figure below, in two separate studies encompassing nearly 20,000 patients, as triglyceride levels increased, so did the risk of a cardiovascular event. In summary, apoC-III impacts triglyceride levels and may also increase inflammatory processes, and this combination of effects makes apoC-III a promising target for reducing the residual CVD risk in patients already on statin therapy, but for whom triglycerides are poorly controlled.



AKCEA-APOCIII-L_{Rx} Commercial Opportunity

ApoC-III levels and elevated triglycerides have been linked to increased cardiovascular risk and lowering apoC-III and triglycerides may reduce this risk. We estimate the eligible population to be greater than 8 million people globally. We believe that positive results from a large cardiovascular outcome study will be required to support marketing authorization for the treatment of these patients. If Novartis exercises its option to license AKCEA-APOCIII-L_{Rx}, it plans to conduct, at its expense, such a study pursuant to our strategic collaboration to conduct this study and to commercialize AKCEA-APOCIII-L_{Rx} for these patients. As part of the collaboration, we may co-commercialize AKCEA-APOCIII-L_{Rx} in selected markets, on mutually agreed terms and conditions.

- *AKCEA-TTR-L_{Rx}*. We are developing AKCEA-TTR-L_{Rx} to treat the broad population of patients with both hereditary and wild-type forms of transthyretin amyloidosis, or ATTR amyloidosis. Based on its profile, we believe AKCEA-TTR-L_{Rx} treatment can significantly reduce levels of the TTR protein, which we believe will translate to efficacy in terms of both clinical benefit and quality of life improvements with a favorable safety and tolerability profile. As with other LICA medicines, we believe we can achieve this positive efficacy, safety and tolerability profile with low doses and with the potential for monthly dosing. We initiated a Phase 1/2 study of AKCEA-TTR-L_{Rx} in the fourth quarter of 2018 and are working toward a goal of initiating the Phase 3 program in 2019.

Disease Background

hATTR amyloidosis is a rare, progressive, and fatal disease that often affects multiple organs, including the nerves, heart, gastrointestinal tract and kidneys. hATTR amyloidosis occurs when misfolded TTR protein deposits throughout the body as amyloid fibrils, disrupting tissue and organ structure and function. The burden of hATTR amyloidosis is high as patients often suffer from progressive neuropathy, cardiac, gastrointestinal and psychosocial symptoms affecting every aspect of their life. Without therapeutic intervention, patient quality of life progressively and rapidly deteriorates, leading to a reduction in ambulation and daily function, and ultimately resulting in premature death. As the disease progresses, many patients are no longer able to work and or are forced to take substantial time off. The impact of the disease is not limited to physical symptoms but also impacts mental health and outlook as patients often live in fear and isolation. An accurate and timely diagnosis and early treatment initiation is critical to optimize disease management.

AKCEA-TTR-L_{Rx} Commercial Opportunity

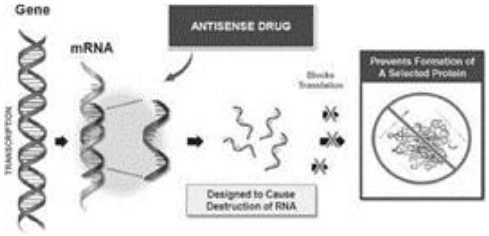
The introduction of new medicines for the ATTR amyloidosis community will increase awareness and diagnosis while AKCEA-TTR-L_{Rx} is being developed. There are currently around 50,000 hATTR amyloidosis patients worldwide and we believe that approximately 60% of patients have symptoms of both polyneuropathy and cardiomyopathy. We believe the number of people with predominant cardiomyopathy symptoms is significantly underdiagnosed. We believe this is especially true in the African American population in which approximately 3% carry the V122I mutation, one of the most dominant mutations causing ATTR. The epidemiology of wild-type TTR amyloidosis is not well characterized, but the number of patients diagnosed is rapidly increasing. It is estimated that there are more than 200,000 diagnosed people with wild-type ATTR.

Technology Overview

Antisense Technology

Ionis discovered each of the drugs in our pipeline using its innovative antisense technology platform. Antisense technology is based on the use of synthetic nucleic acid sequences, which are primarily used to interrupt the production of a specified protein by targeting the specific corresponding messenger RNA, or mRNA, that encodes that protein. In this way, antisense drugs can be used to reduce the level of proteins that cause, or contribute to, the progression of various diseases. Because there are virtually no undruggable mRNA targets, we believe antisense technology may have broader potential than small molecule- and antibody-based technologies that target proteins. Furthermore, antisense technology has the potential to target a growing number of disease-related genes more directly and efficiently than other protein-directed modalities. We believe this technology represents an important advance in treating diseases.

The production of a protein starts with a process called transcription, where the instructions for making a protein are transcribed from a gene, or DNA, into mRNA. The cell's protein production process is called translation, and antisense drugs can be designed to interrupt this process by causing the destruction of the targeted mRNA and therefore preventing the production of a protein of interest. The graphic below further illustrates the impact of antisense drugs on the production of proteins via this mechanism of action:



Ionis has made significant improvements in its antisense drug technology in recent years, most notably the creation of the advanced ligand conjugated antisense, or LICA technology. Other improvements include the discovery screening processes, which resulted in second-generation drugs with better safety and tolerability properties compared to Ionis' generation 2.0 drugs. These improved second-generation drugs are referred to as generation 2+ drugs.

The unique properties of our antisense drugs provide several potential advantages over traditional drug modalities. These advantages include:

- ***Precise specificity***. Our antisense drugs are created using Ionis' generation 2+ screening processes to bind specifically to the mRNAs they were designed to target, which minimizes or eliminates the possibility of our drugs binding to unintended genetic targets and causing unwanted side effects.
- ***Favorable dosing properties***. We believe our drugs have predictable safety, pharmacokinetic and pharmacodynamic properties based on Ionis' research and development experience. Further, our drugs have a relatively long half-life of two to four weeks, which enables second generation drugs such as WAYLIVRA to be dosed once weekly and other drugs in our pipeline, which incorporate Ionis' LICA technology, to potentially be dosed once monthly or less frequently. Upon dosing, our drugs distribute well throughout the body, eliminating the need for special formulations or delivery vehicles.
- ***No anticipated drug-to-drug interactions***. Because they are nucleic acid based, we believe our drugs can be used in combination with virtually any existing treatment modality without the risk of drug-to-drug interactions or susceptibility to traditional enzyme degradation or metabolism pathways.
- ***Broad applications to multiple disease targets, multiple tissues and multiple mechanisms***. There are virtually no "undruggable" targets with antisense technology.
- ***Efficient discovery and early development***. Because of the efficiency of antisense technology, drug discovery and early development costs and success rates compare favorably to small molecule or antibody drug discovery and development.

Our Relationship with Ionis

Ionis formed Akcea as a wholly owned subsidiary to complete development of and commercialize Ionis' drugs to treat lipid disorders. We began business operations in January 2015. We licensed our cardiometabolic franchise from Ionis at the beginning of 2015. Prior to licensing these drugs, Ionis' employees performed all of the development, regulatory and manufacturing activities for these drugs either themselves or through third-party providers. As such, Ionis incurred all of the expenses associated with these activities and reported them in its consolidated financial statements. We licensed TEGSEDI and AKCEA-TTR-L $_{Rx}$ from Ionis in April 2018. Prior to then, Ionis had been advancing these drugs in development and incurring the expenses for those activities. Under our license agreements with Ionis, Ionis continued and is continuing to conduct development, regulatory or manufacturing activities for most of our drugs and to charge us for this work. As of December 31, 2018, Ionis owned approximately 75 percent of our outstanding stock.

Exclusive Rights to Development Pipeline and Intellectual Property; Right of First Negotiation

Ionis is the leading company researching and developing antisense drugs. Under our agreements with Ionis, we have rights to Ionis' proprietary technologies for use with our drugs. Specifically, we obtained an exclusive license from Ionis to globally commercialize our pipeline of drugs, including TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$, AKCEA-APOCIII-L$_{Rx}$ and AKCEA-TTR-L$_{Rx}$. Ionis also agreed that it would not work on its own or with other parties to develop or commercialize antisense drugs that target the same gene targets as the drugs we are developing and commercializing. Under our agreements with Ionis, we have a license to use Ionis' technology platform with our drugs. We also have access to future improvements Ionis may make to its antisense technology platform, such as improved manufacturing technologies.

In addition, Ionis has granted us a right of first negotiation with respect to Ionis development candidates that are designed to treat a rare cardiometabolic disease or a rare inherited metabolic disease.

Our Strategic Collaboration with Novartis

In January 2017, we initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L$_{Rx}$. Novartis is currently preparing to initiate a Phase 3 study of AKCEA-APO(a)-L$_{Rx}$ in patients with established cardiovascular disease (CVD) and elevated levels of lipoprotein(a), or Lp(a). Novartis is now responsible for all future development and commercialization activities for AKCEA-APO(a)-L$_{Rx}$. We are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APO(a)-L$_{Rx}$ from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. In connection with Novartis' exercise of its option to exclusively license AKCEA-APO(a)-L$_{Rx}$, Akcea and Novartis established a more definitive framework under which they would negotiate the co-commercialization of AKCEA-APO(a)-L$_{Rx}$ between the two companies in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L$_{Rx}$ in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L$_{Rx}$. We will share any license fees, milestone payments and royalties equally with Ionis.

Under the strategic collaboration, option and license agreement, Novartis also has an exclusive option to develop and commercialize AKCEA-APOCIII-L_{Rx}. We are responsible for completing a Phase 2 program and conducting an end-of-Phase 2 meeting with the FDA for AKCEA-APOCIII-L_{Rx} and delivering API. Following the successful completion of the Phase 2 program, and prior to initiation of the Phase 3 study, Novartis will be able to exercise its option to license and commercialize AKCEA-APOCIII-L_{Rx}. Novartis will have 60 days plus additional time that could be required for Hart-Scott-Rodino, or HSR, filing and review following the end-of-Phase 2 meeting to exercise its option for AKCEA-APOCIII-L_{Rx}. If Novartis exercises its option, Novartis will be responsible, at its expense, to use commercially reasonable efforts to develop and commercialize AKCEA-APOCIII-L_{Rx}.

From this collaboration, we received $75.0 million in an upfront option payment, of which we retained $60.0 million and paid Ionis $15.0 million as a sublicense fee under our license agreement with Ionis. In conjunction with this collaboration, Novartis purchased $100.0 million of Ionis' common stock at a premium. We also earned a $150.0 million license fee when Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} of which we will pay $75.0 million to Ionis as a sublicense fee. The $75.0 million obligation to Ionis will be settled in Akcea common stock. During the years ended December 31, 2018 and 2017, we recognized $50.6 million and $43.4 million of revenue related to our Novartis collaboration, respectively.

In addition, for AKCEA-APO(a)-L_{Rx}, we are eligible to receive up to $675.0 million in milestone payments, including $25.0 million for the achievement of a development milestone, up to $290.0 million for the achievement of regulatory milestones and up to $360.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, we are eligible to receive a license fee of $150.0 million and up to $530.0 million in milestone payments, including $25.0 million for the achievement of a development milestone, up to $240.0 million for the achievement of regulatory milestones and up to $265.0 million for the achievement of commercialization milestones. We will earn the next milestone payment of $25.0 million under this collaboration if Novartis advances the Phase 3 study for either drug. We are also eligible to receive tiered royalties in the mid-teens to low-twenty percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. We will pay 50% of these license fees, milestone payments and royalties to Ionis as a sublicense fee.

For each product Novartis commercializes under this agreement, we may co-commercialize with Novartis in selected markets, through our specialized sales force, on terms and conditions that we plan to negotiate with Novartis in the future.

If Novartis does not exercise its option, or stops developing or commercializing after exercising its option with respect to a particular drug, we will have all rights to develop or commercialize the drug (including the right to sublicense these rights to a third party) at our sole expense. If Novartis stops developing or commercializing a drug after exercising its option, and we subsequently commercialize the drug on our own or with another party, we are required to negotiate in good faith and mutually agree with Novartis the terms of a royalty payable to Novartis on the returned drug.

The agreement with Novartis will continue until the earlier of the date that all of Novartis' options to obtain the exclusive licenses under the agreement expire unexercised or, if Novartis exercises its options, until the expiration of all payment obligations under the agreement. In addition, the agreement as a whole or with respect to any drug under the agreement may terminate early under the following situations:

- Novartis may terminate the agreement as a whole or with respect to any drug at any time by providing written notice to us;
- Either we or Novartis may terminate the agreement with respect to any drug by providing written notice to the other party in good faith that we or Novartis have determined that the continued development or commercialization of the drug presents safety concerns that pose an unacceptable risk or threat of harm in humans or would violate any applicable law, ethical principles or principles of scientific integrity;
- Either we or Novartis may terminate the agreement for a drug by providing written notice to the other party upon the other party's uncured failure to perform a material obligation related to the drug under the agreement, or the entire agreement if the other party becomes insolvent; and
- We may terminate the agreement if Novartis disputes or assists a third party to dispute the validity of any of our or Ionis' patents.

Additionally, in January 2017, we and Ionis entered into a Stock Purchase Agreement, or SPA, with Novartis. Under the SPA, in July 2017, Novartis purchased $50.0 million of our common stock in a separate private placement concurrent with the completion of our IPO at a price per share equal to the IPO price.

Competition

The commercialization of new drugs is competitive, and we may face worldwide competition from major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, nutraceutical companies and ultimately generic companies. Our competitors may develop or market therapies that are more effective, safer, more convenient to use, or less costly than any that we are commercializing, or may obtain regulatory or reimbursement approval for their therapies more rapidly than we may obtain approval for ours. Many of our competitors have substantially greater financial, technical and human resources than we have. Additionally, mergers and acquisitions in the pharmaceutical industry may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances made in the commercial applicability of technologies and greater availability of capital for investment in these fields.

With respect to TEGSEDI and AKCEA-TTR-L_{Rx}, ONPATTRO (patisiran), which is an RNAi therapy made by Alnylam, is currently marketed for hATTR amyloidosis with polyneuropathy in the U.S. and E.U. The product label for TEGSEDI in the United States has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Though ONPATTRO requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. In addition, Tafamidis is currently available in the E.U. for stage 1 hATTR amyloidosis with polyneuropathy, and is currently under review in the U.S. for ATTR with cardiomyopathy, with a PDUFA date in July 2019. Beyond these drugs that are either marketed or under regulatory review, there are also additional drugs in clinical development. Alnylam is developing next generation RNAi drug vutrisiran which is currently in Phase 3 clinical development in hATTR amyloidosis with polyneuropathy, with plans to move into cardiomyopathy. Eidos is developing AG10 for patients with ATTR with cardiomyopathy and has recently completed Phase 2, with plans to move into Phase 3.

With respect to WAYLIVRA to treat patients with FCS, Gemphire's Gemcabene is being studied in patients with severe hypertriglyceridemia, defined as triglycerides above 500 mg/dL. Gemphire announced in June 2018 that Gemcabene met its Phase 2b primary endpoint and demonstrated statistically significant lowering of triglycerides in SHTG. In August 2018, however, the FDA has requested that Gemphire produce data from a sub-chronic toxicology study to lift the partial clinical hold that was issued in 2004 (The FDA issued the partial clinical hold as PPAR agonists are potential liver toxins). The initiation of Phase 3 will not take place until the partial hold is lifted and Gemphire has announced that it plans to conduct these required studies and expects to submit the additional results to the FDA in the second quarter of 2019.

Metreleptin is in a Phase 3 trial for FPL patients who also have NASH. Metreleptin is currently approved for use in the U.S. and E.U. in generalized lipodystrophy, or GL patients. Metreleptin does not affect apoC-III levels. ApoC-III levels have been shown to be elevated in FPL patients and directly correlated to triglyceride levels. In addition, many patients with FCS and FPL use diet, niacin, fish oils and/or fibrates to reduce their elevated triglycerides. Niacin, fish oils and fibrates are generally not effective in patients with FCS. The ultra-low-fat diet that patients with FCS and FPL are required to maintain is extremely burdensome to patients and their families. Based on our WAYLIVRA clinical experience, including in individuals with FCS, we believe that WAYLIVRA will work equally well as a single agent or in combination with other triglyceride-lowering drugs or approaches.

With respect to WAYLIVRA and AKCEA-APOCIII-L_{Rx}, in January 2019, Arrowhead filed for regulatory clearance to begin Phase 1 study of ARO-APOC3, an RNAi-based drug targeting apoC-III for treatment of hypertriglyceridemia. Arrowhead has announced that it intends to proceed with this Phase 1 single and multiple dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ARO-APOC3 in adult healthy volunteers, hypertriglyceridemic patients, and patients with FCS. To our knowledge, there are currently no other direct competitors for lowering apoC-III in clinical development.

With respect to AKCEA-APO(a)-L_{Rx}, we are not aware of any other drugs currently in clinical development specifically for the treatment of hyperlipoproteinemia(a) and associated cardiovascular disease. Arrowhead and Amgen have a Phase 1 program ongoing for AMG890, formerly referred to as ARO-LPA, which uses an RNAi drug conjugated with a GalNAc for the same target as AKCEA-APO(a)-L_{Rx} . Under its strategic collaboration agreement with Alnylam Pharmaceuticals, Inc., or Alnylam, Ionis received an exclusive, royalty-bearing license to Alnylam's chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against apo(a), which means that Alnylam agreed not to use the exclusively licensed technology to develop or commercialize an oligonucleotide against apo(a).

AKCEA-ANGPTL3-L_{Rx} may compete with Evinacumab, a monoclonal antibody that binds to ANGPTL3 that Regeneron Pharmaceuticals, Inc. is developing. Evinacumab is currently in Phase 2 development for the treatment of HoFH and severe forms of hyperlipidemia. Additionally, many patients with familial hyperlipidemias are treated using diet and statins, which have limited effect in these patients.

Intellectual Property

We have in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to WAYLIVRA, AKCEA-APO(a)-L_{Rx}, our other drugs in development and, more generally, the development and commercialization of oligonucleotide therapeutics. Our objective is to continue to develop and strengthen our proprietary position to further protect our drugs.

We obtained our rights to the patents covering WAYLIVRA, AKCEA-APO(a)-L_{Rx} and our other drugs in development and our rights in Ionis' proprietary technology platform and know-how under our development, commercialization and license agreement with Ionis. We seek to expand our portfolio of patents and patent applications by filing and prosecuting existing patent rights and filing additional patent applications.

We seek patent protection in significant markets and/or countries for each drug in development. We also seek to maximize patent term. The patent exclusivity period for a drug will prevent generic drugs from entering the market. Patent exclusivity depends on a number of factors, including initial patent term and available patent term extensions based upon delays caused by the regulatory approval process.

TTR, TEGSEDI and AKCEA-TTR-L_{Rx} Intellectual Property

We have an exclusive license under Ionis' TTR patent estate to develop and commercialize TEGSEDI and the LICA follow-on drug AKCEA-TTR-L_{Rx}.

The TTR patent estate includes granted US patents covering the TEGSEDI compound, composition, and uses (e.g. US 8,101,743; US 8,697,860; US 9,061,044; and US 9,399,774) that together provide natural patent term to 2031. We have applied for patent term extension to recapture a portion of the term lost during regulatory review. The issued claims protect TEGSEDI from generic competition in the United States until at least 2031. Similar patents covering TEGSEDI are granted in several foreign jurisdictions including Europe and Japan.

The TTR patent estate also includes granted and pending claims covering AKCEA-TTR-L_{Rx} worldwide. Granted claims in Europe cover the sequence of AKCEA-TTR-L_{Rx} and its use in treating transthyretin amyloidosis with natural patent term to 2031 (EP2563920). Claims covering the specific chemical composition of AKCEA-TTR-L_{Rx} and use in treating transthyretin amyloidosis are pending and have natural patent term to 2034 excluding any additional term adjustments or patent term extensions.

ApoC-III, WAYLIVRA and AKCEA-APOCIII-L_{Rx} Intellectual Property

We have an exclusive license under Ionis' apoC-III patent estate to develop and commercialize WAYLIVRA and the LICA follow-on drug AKCEA-APOCIII-L_{Rx}. The apoC-III patent estate includes patent claims in the United States drawn to the use of antisense compounds complementary to the mRNA of human apoC-III, including compounds designed to the region targeted by WAYLIVRA and AKCEA-APOCIII-L_{Rx} (US 7,598,227) which, excluding any additional term adjustments or patent term extensions, expires in 2023. Similar claims covering compounds complementary to any site on human apoC-III have granted in Australia.

The apoC-III patent estate also includes issued patent claims to the specific antisense sequence and chemical composition of WAYLIVRA in the United States (US 7,750,141), Australia and Europe (EP1622597). The issued claims in the United States should protect WAYLIVRA from generic competition in the United States until at least 2023. In addition, depending upon the timing, duration and specifics of FDA regulatory review, this patent may be eligible for patent term restoration to recapture a portion of the term lost during such review. We are also pursuing additional patent applications directed to methods of using WAYLIVRA and other apoC-III compounds for treating various disorders, including FCS in jurisdictions worldwide. Claims drawn to methods of using apoC-III specific inhibitors, and specifically compounds designed to target the same sequence as WAYLIVRA and AKCEA-APOCIII-L_{Rx}, for treating FCS have issued in the United States (US 9,593,333) and will expire in 2034, excluding any additional term adjustments or patent term extensions.

The apoC-III patent estate also includes issued patent claims covering the specific chemical composition of AKCEA-APOCIII-L_{Rx} in the United States (US 9,163,239). The claims should protect AKCEA-APOCIII-L_{Rx} from generic competition until at least 2034. We are pursuing additional patent coverage for AKCEA-APOCIII-L_{Rx} in jurisdictions worldwide.

Apo(a) and AKCEA-APO(a)-L_{Rx} Intellectual Property

We have an exclusive license under Ionis' apo(a) patent estate to develop and commercialize AKCEA-APO(a)-L_{Rx}. The apo(a) patent estate includes issued patent claims to the specific antisense sequence and chemical composition of AKCEA-APO(a)-L_{Rx} in the United States (US 9,181,550). The issued claims directed to the composition should protect AKCEA-APO(a)-L_{Rx} from generic competition in the United States until at least 2034. In addition, patent term restoration may be available to recapture a portion of the term lost during FDA regulatory review. We are also pursuing additional patent applications designed to protect the AKCEA-APO(a)-L_{Rx} composition and additional dosing and methods of use in jurisdictions worldwide.

ANGPTL3 and AKCEA-ANGPTL3-L_{Rx} Intellectual Property

We have an exclusive license under Ionis' ANGPTL3 patent estate to develop and commercialize AKCEA-ANGPTL3-L_{Rx}. The ANGPTL3 patent estate includes issued patent claims drawn to the use of antisense compounds complementary to ANGPTL3 RNA for inhibiting the production of ANGPTL3 (US 8,653,047). The ANGPTL3 patent estate also includes issued patent claims covering the specific antisense sequence and chemical composition of AKCEA-ANGPTL3-L_{Rx} in the United States (US 9,382,540). The issued claims directed to the chemical composition should protect AKCEA-ANGPTL3-L_{Rx} from generic competition until at least 2035. We are pursuing additional patent claims designed to protect the sequence and chemical composition of AKCEA-ANGPTL3-L_{Rx} in jurisdictions worldwide.

Trade Secrets

In addition to the protections afforded by patents and other regulatory protections, we may rely, in some circumstances, on trade secrets to protect our technology. Trade secrets may be useful to protect proprietary know-how that is not patentable or which we elect not to patent. Trade secrets may also be useful for processes or improvements for which patents are difficult to enforce. We also protect our drugs and the proprietary technology platform by confidentiality agreements with employees, consultants, advisors, contractors and collaborators. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

Manufacturing

Ionis has dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since Ionis can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide drugs, we and Ionis found that the same techniques used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. With Ionis' expertise in optimizing manufacturing of oligonucleotides, we and Ionis believe we can develop new processes to scale up manufacturing of our LICA medicines at commercially competitive prices. By developing several proprietary chemical processes to scale up our manufacturing capabilities, Ionis has greatly reduced the cost of producing oligonucleotide drugs. For example, they have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing capacity to make the drugs. Through both Ionis' internal research and development programs and collaborations with outside vendors we and Ionis may achieve even greater efficiency and further cost reductions. In connection with Novartis' exercise of its option to license AKCEA-APO(a)-L_{Rx}, and if Novartis exercises its option to license AKCEA-APOCIII-L_{Rx}, Novartis will be responsible for the long-term supply of drug substance and finished drug product for the licensed drug.

TEGSEDI

For TEGSEDI's commercial drug supply, we are using contract manufacturing organizations, or CMOs, to produce custom raw materials, active pharmaceutical ingredient, or API, and finished goods. Our CMO partners have extensive technical expertise and current good manufacturing practice, or cGMP, experience. We believe our current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands. Additionally, we continue to evaluate relationships with additional suppliers to increase overall capacity as well as reduce further risks. While we believe that there are alternate sources of supply that can satisfy our commercial requirements, we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs. We also cannot provide assurance that we will not experience a disruption in supply from our current CMO partners.

CMOs are subject to the FDA's cGMP requirements and other rules and regulations prescribed by foreign regulatory authorities. We depend on our CMO partners for continued compliance with cGMP requirements and applicable foreign standards.

WAYLIVRA

Ionis has supplied us with API and finished drug product to complete our ongoing activities for WAYLIVRA through either Ionis' own manufacturing processes or through outside vendors. Ionis has also supplied the API and the finished drug product for WAYLIVRA's commercial launch, if approved. We believe the API and drug product is adequate for at least the first two years of WAYLIVRA's commercial launch. We plan to leverage our relationships with CMOs, to procure our own long-term raw material and drug supplies at competitive prices in the future.

LICA Pipeline

We believe we have sufficient manufacturing capacity, through Ionis, to meet our current development needs, including the ongoing studies for AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated future needs. Ionis has supplied the API and the finished drug product for the clinical studies for each of the drugs in our pipeline through the completion of the on-going studies. Ionis also has agreed to supply and has supplied the API and the finished drug product for our drugs. We and Ionis have long-standing and strong relationships with third-party vendors who can supply us with both API and finished drug product and are currently supplying API and finished drug product to other of Ionis' partners. Ionis also has long-standing and strong relationships with the vendors who supply the key raw materials to Ionis to make our drugs and to a major oligonucleotide CMO. We also believe that with anticipated benefits from increases in scale and improvements in chemistry, through Ionis or third parties, we will be able to manufacture our antisense drugs at commercially reasonable prices.

For LICA-conjugated drugs, to date, Ionis has manufactured itself or through a contract manufacturing organization only limited supplies of LICA for their own and our own nonclinical and clinical studies. LICA enables lower doses than unconjugated oligonucleotides. Along with Ionis' expertise in optimizing manufacturing of oligonucleotides, we believe this will enable the development of new processes to scale up manufacturing of these LICA conjugated drugs at commercially competitive prices.

Government Regulation and Approval

United States—FDA Process

In the United States, the FDA regulates drugs. The Federal Food, Drug and Cosmetic Act, or FDCA, and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of drugs. To obtain regulatory approvals in the United States and in foreign countries, and subsequently comply with applicable statutes and regulations, we will need to spend substantial time and financial resources.

Approval Process

The FDA must approve any new unapproved drug or certain changes to a previously approved drug before a manufacturer can market it in the United States. If a company does not comply with applicable United States requirements, it may be subject to a variety of administrative or judicial sanctions, such as FDA refusal to approve pending applications, Warning or Untitled Letters, clinical holds, drug recalls, drug seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution. The steps we must complete before we can market a drug include:

- completion of preclinical laboratory tests, animal studies, and formulation studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical studies start. The sponsor must update the IND annually;
- approval of the study by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical study begins;
- performance of adequate and well-controlled human clinical studies to establish the safety and efficacy of the drug for each indication to the FDA's satisfaction;
- submission to the FDA of an NDA;
- potential review of the drug application by an FDA advisory committee, where appropriate and if applicable;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities to assess compliance with current good manufacturing practices, cGMP, or regulations; and
- FDA review and approval of the NDA.

It generally takes companies many years to satisfy the FDA approval requirements, but this varies substantially based upon the type, complexity and novelty of the drug or disease. Preclinical tests include laboratory evaluation of a drug's chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the drug. The conduct of the preclinical tests must comply with federal regulations and requirements, including GLP. The company submits the results of the preclinical testing to the FDA as part of an IND along with other information, including information about the drug's chemistry, manufacturing and controls, and a proposed clinical study protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after submitting the initial IND.

The FDA requires a 30-day waiting period after the submission of each IND before a company can begin clinical testing in humans in the United States. If the FDA has neither commented on nor questioned the IND within this 30-day period, the IND sponsor may begin the proposed clinical study. However, the FDA may, within the 30-day time period, raise concerns or questions relating to one or more proposed clinical studies and place the clinical study on a clinical hold. In such a case, the company and the FDA must resolve any outstanding concerns before the company begins the clinical study. Accordingly, the submission of an IND may or may not be sufficient for the FDA to permit the sponsor to start a clinical study. The company must also make a separate submission to an existing IND for each successive clinical study conducted during drug development.

Clinical Studies

Clinical studies involve administering the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. The company must conduct clinical studies:

- in compliance with federal regulations;
- in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical study sponsors, administrators and monitors; and
- under protocols detailing the objectives of the trial, the safety monitoring parameters and the effectiveness criteria.

The company must submit each protocol involving testing on United States patients and subsequent protocol amendments to the FDA as part of the IND. The FDA may order the temporary, or permanent, discontinuation of a clinical study at any time, or impose other sanctions, if it believes that the sponsor is not conducting the clinical study in accordance with FDA requirements or presents an unacceptable risk to the clinical study patients. The sponsor must also submit the study protocol and informed consent information for patients in clinical studies to an IRB for approval. An IRB may halt the clinical study, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Companies generally divide the clinical investigation of a drug into three or four phases.

- *Phase 1.* The company evaluates the drug in healthy human subjects or patients with the target disease or condition. These studies typically evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational new drug in humans, the side effects associated with increasing doses and, if possible, gain early evidence on effectiveness.
- *Phase 2.* The company administers the drug to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks and preliminarily evaluate efficacy.
- *Phase 3.* The company administers the drug to an expanded patient population, generally at geographically dispersed clinical study sites, to generate enough data to statistically evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational drug and to provide an adequate basis for product approval.
- *Phase 4.* In some cases, the FDA may condition approval of an NDA for a drug on the company's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. We typically refer to such post-approval studies as Phase 4 clinical studies.

While companies usually conduct these phases sequentially, they are sometimes overlapped or combined. A combined phase trial, such as a Phase 1/2 or a Phase 2/3 trial, is one that combines elements of objectives from two ordinarily sequential phases of development. For example, in a Phase 1/2 trial, the objectives may include both dose-finding and initial efficacy. In a Phase 2/3 trial, dosing regimen or population selection objectives are combined with confirmation of the safety and efficacy of the administration schedule in the intended population.

A pivotal study is a clinical study that adequately meets regulatory agency requirements to evaluate a drug's efficacy and safety to justify the approval of the drug. Generally, pivotal studies are Phase 3 studies, but the FDA may accept results from Phase 2 studies if the study design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations in which there is an unmet medical need and the results are sufficiently robust.

The FDA, the IRB or the clinical study sponsor may suspend or terminate a clinical study at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board or committee, may oversee some clinical studies. This group provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical study based on evolving business objectives and the competitive climate.

Submission of an NDA

After we complete the required clinical testing, we can prepare and submit an NDA to the FDA, which must approve the NDA before we can start marketing the drug in the United States. An NDA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the drug's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical studies on a drug, or from a number of alternative sources, including studies initiated by investigators. To support marketing authorization, the data we submit must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug to the FDA's satisfaction.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved new drug application are also subject to annual program user fees. The FDA typically increases these fees annually. Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages and user-fee waivers.

The FDA has 60 days from its receipt of an NDA to determine whether it will accept the application for filing based on the agency's threshold determination that the application is sufficiently complete to permit substantive review. Once the FDA accepts the filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Under the Prescription Drug User Fee Act, the FDA has a goal of responding to standard review NDAs within ten months after the 60-day filing review period, but this timeframe is often extended. The FDA reviews most applications for standard review drugs within ten to 12 months and most applications for priority review drugs within six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists.

The FDA may also refer applications for novel drugs that present difficult questions of safety or efficacy to an advisory committee. This is typically a panel that includes clinicians and other experts that will review, evaluate and recommend whether the FDA should approve the application. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP and will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the drug unless compliance with cGMP is satisfactory and the NDA contains data that provide evidence that the drug is safe and effective in the indication studied.

The FDA's Decision on an NDA

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter indicates that the FDA has completed its review of the application and the agency has determined that it will not approve the application in its present form. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional clinical data and/or other significant, expensive and time-consuming requirements related to clinical studies, preclinical studies and/or manufacturing. The FDA has committed to reviewing resubmissions of the NDA addressing such deficiencies in two or six months, depending on the type of information included. Even if we submit such data, the

FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Also, the government may establish additional requirements, including those resulting from new legislation, or the FDA's policies may change, which could delay or prevent regulatory approval of our drugs under development.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patient registries. The requirement for REMS can materially affect the potential market and profitability of the drug. Moreover, the FDA may condition approval on substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, the FDA may withdraw drug approvals if the company fails to comply with regulatory standards or identifies problems following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before we can implement the change. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing new NDAs. As with new NDAs, the FDA often significantly extends the review process with requests for additional information or clarification.

Expedited review and accelerated approval programs

A sponsor may seek approval of its drug candidate under programs designed to accelerate the FDA's review and approval of NDAs. For example, the FDA may grant Fast Track Designation to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of Fast Track Designation are the eligibility for priority review, rolling review (submission of portions of an application before the complete marketing application is submitted), and accelerated approval, if the application meets relevant criteria. Based on results of the Phase 3 clinical study(ies) submitted in an NDA, upon the request of an applicant, the FDA may grant the NDA a priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. The FDA grants priority review where there is evidence that the proposed drug would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If the criteria for priority review are not met, the application is subject to the standard FDA review period of ten months after the FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve an NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, 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. The FDA generally requires post-marketing studies or completion of ongoing studies after marketing authorization to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, a sponsor may seek FDA designation of its drug candidate as a breakthrough therapy if the drug can, alone or in combination with one or more other drugs, treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Post-approval Requirements

The FDA regulates drugs that we manufacture or distribute pursuant to FDA approvals and has specific requirements pertaining to recordkeeping, periodic reporting, drug sampling and distribution, advertising and promotion and reporting of adverse experiences with the drug. After approval, the FDA must provide review and approval for most changes to the approved drug, such as adding new indications or other labeling claims. There also are continuing, annual program user fee requirements for any marketed drugs, as well as new application fees for supplemental applications with clinical data.

In some cases, the FDA may condition approval of an NDA for a drug on the sponsor's agreement to conduct additional clinical studies after approval. In other cases, a sponsor may voluntarily conduct additional clinical studies after approval to gain more information about the drug. We typically refer to such post-approval studies as Phase 4 clinical studies.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements. There are strict regulations regarding changes to the manufacturing process, and depending on the significance of the change, it may require prior FDA approval before we can implement it. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our drugs and we expect to rely in the future on third parties for the production of commercial quantities. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a drug or the failure to comply with applicable requirements may result in restrictions on a drug, manufacturer or holder of an approved NDA, including withdrawal or recall of the drug from the market or other voluntary, FDA-initiated or judicial actions that could delay or prohibit further marketing.

The FDA may withdraw approval if a company does not comply with regulatory requirements and maintain standards or if problems occur after the drug reaches the market. If a company or the FDA discovers previously unknown problems with a drug, including adverse events of unanticipated severity or frequency, issues with manufacturing processes or the company's failure to comply with regulatory requirements, the FDA may require revisions to the approved labeling to add new safety information; impose post-marketing studies or other clinical studies to assess new safety risks; or impose distribution or other restrictions under a REMS program. Other potential consequences may include:

- restrictions on the marketing or manufacturing of the drug, complete withdrawal of the drug from the market or drug recalls;
- fines, warning letters or holds on post-approval clinical studies;
- the FDA refusing to approve pending NDAs or supplements to approved NDAs, or suspending or revoking drug license approvals;
- drug seizure or detention, or refusal to permit the import or export of drugs; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of drugs 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. We could be subject to significant liability if we violated these laws and regulations.

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the United States.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical study costs, tax advantages and user-fee waivers. In addition, if a drug receives FDA approval for the indication for which it has orphan designation, the drug has orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the drug with orphan exclusivity.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which the FDA has granted an orphan designation.

U.S. Patent Term Restoration

Patent term can also be extended based on the amount of time the patented drug spends in regulatory review for drug approval. The length of time between drug launch and patent expiration is significantly less than the full 20-year patent term because companies often obtain the patents relating to a drug early in development and the development path for regulatory approval is long. In the United States, The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act) permits a patent holder to seek a patent extension, commonly called patent term restoration, for a patent on a drug governed by the FDCA. The length of patent term restoration is related to the length of time the drug is under regulatory review. Patent term restoration can be a maximum of 5 years and cannot extend the remaining term of a patent beyond a total of 14 years from the date of drug approval. Only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug in that jurisdiction.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Act, 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 abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order to approve an ANDA, 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 RLD. Under the statute, a generic drug is bioequivalent to an RLD if "the rate and extent of absorption of the generic 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 that the generic drug is "therapeutically equivalent" to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider an "AB" therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of an "AB" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

The FDCA provides a period of five years of non-patent 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 that were conducted by or for the applicant and are essential to the approval of the application, and are not bioavailability or bioequivalence studies. This three-year exclusivity period often protects changes to a previously approved drug, 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 must list with the FDA each patent with claims that cover the applicant's drug or a method of using the drug. 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 drug in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. 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 drug.

A certification that the new drug will not infringe the already approved drug'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 indicates that it is not seeking approval of a patented method of use, the FDA will not approve the ANDA application until all the listed patents claiming the referenced drug have expired.

If the ANDA 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.

Disclosure of Clinical Study Information

Sponsors of clinical studies of FDA-regulated products, including drugs, are required to register and disclose certain clinical study information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical study is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical studies after completion. Disclosure of the results of these studies can be delayed until the new drug or new indication being studied has been approved. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Healthcare Reform

In the United States and foreign jurisdictions, the legislative landscape continues to evolve. There have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the United States federal and state levels that seek to reduce healthcare costs. In March 2010, the Patient Protection and Affordable Care Act, or PPACA, was enacted, which includes measures that have significantly changed health care financing by both governmental and private insurers. The provisions of the PPACA of importance to the pharmaceutical and biotechnology industry are, among others, the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, unless the drug is subject to discounts under the 340B drug discount program;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- new requirements under the federal Physician Payments Sunshine Act for drug manufacturers to report information related to payments and other transfers of value made to physicians and teaching hospitals as well as ownership or investment interests held by physicians and their immediate family members; and
- a new requirement to annually report certain drug samples that manufacturers and distributors provide to licensed practitioners, or to pharmacies of hospitals or other healthcare entities.

Since its enactment there have been judicial and Congressional challenges to or proposals to amend certain aspects of PPACA. We expect there will be additional challenges and amendments to it in the future.

In addition, other health reform measures have been proposed and adopted in the United States since PPACA was enacted. For example, as a result of the Budget Control Act of 2011, providers are subject to Medicare payment reductions of 2% per fiscal year through 2025 unless additional Congressional action is taken. Further, the American Taxpayer Relief Act of 2012 reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments from providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.

European Union—EMA Process

In the European Union, drugs follow a similar demanding process as that we described above for the United States and the ICH Common Technical Document is the basis for applications. Prior to submitting a European Marketing Authorization Application, or MAA, it is necessary to gain approval of a detailed Pediatric Investigation Plan, or PIP, with the European Medicines Agency's Pediatric Committee, or PDCO. After gaining PIP approval, EU regulatory authorities can authorize the drug using either the centralized authorization procedure or national authorization procedures.

Centralized Procedure

Under the centralized procedure, after the EMA issues an opinion, the European Commission issues a single marketing authorization valid across the European Union, as well as Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for human drugs that: are derived from biotechnology processes, such as genetic engineering; contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions; and are officially designated orphan drugs. For drugs that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the EMA, as long as the drug concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health. WAYLIVRA has been granted a Promising Innovative Medicine, or PIM, Designation by the United Kingdom's Medicines and Healthcare products Regulatory Agency, or MHRA, for the treatment of people with FCS. A PIM Designation is an early indication that a medicinal product is a promising candidate for the Early Access to Medicines Scheme, or EAMS, in the UK, intended for the treatment, diagnosis or prevention of a life-threatening or seriously debilitating condition, with the potential to address an unmet medical need.

National Authorization Procedures

There are also two other possible routes to authorize medicinal products in several countries, which are available for products that fall outside the scope of the centralized procedure:

- Decentralized procedure. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of a medicinal product that has not yet been authorized in any European Union country and that does not fall within the mandatory scope of the centralized procedure.
- Mutual recognition procedure. In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, in accordance with the national procedures of that country. Thereafter, further marketing authorizations can be sought from other European Union countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

Good Manufacturing Practices

Like the FDA, the EMA, the competent authorities of the European Union Member States, and other regulatory agencies regulate and inspect equipment, facilities and processes used in the manufacturing of drugs prior to approving a drug. If, after receiving clearance from regulatory agencies, a company makes a material change in manufacturing equipment, location or process, additional regulatory review and approval may be required. Once we or our partners commercialize drugs, we will be required to comply with cGMP and drug-specific regulations enforced by the European Commission, the EMA and the competent authorities of European Union Member States following drug approval. Also like the FDA, the EMA, the competent authorities of the European Union Member States, and other regulatory agencies also conduct regular, periodic visits to re-inspect equipment, facilities and processes following the initial approval of a drug. If, as a result of these inspections, the regulatory agencies determine that our or our partners' equipment, facilities, or processes do not comply with applicable regulations and conditions of drug approval, they may seek civil, criminal or administrative sanctions and/or remedies against us, including the suspension of our manufacturing operations or the withdrawal of our drug from the market.

Data and Market Exclusivity

Similar to the United States, there is a process to authorize generic versions of innovative drugs in the European Union. Generic competitors can submit abridged applications to authorize generic versions of drugs authorized by EMA through a centralized procedure referencing the innovator's data and demonstrating bioequivalence to the reference drug, among other things. New drugs in the European Union can receive eight years of data exclusivity coupled with two years of market exclusivity, and a potential one-year extension, if the marketing authorizations holder obtains an authorization for one or more new therapeutic indications that demonstrates "significant clinical benefit" in comparison with existing therapies. This system is usually referred to as "8+2." Abridged applications cannot rely on an innovator's data until after expiry of the eight-year date exclusivity term, meaning that a competitor can file an application for a generic drug, but the drug cannot be marketed until the end of the market exclusivity term.

Other International Markets—Drug Approval Process

In some international markets (such as China or Japan), although data generated in United States or European Union studies may be submitted in support of a marketing authorization application, regulators may require additional clinical studies conducted in the host territory, or studying people of the ethnicity of the host territory, prior to the filing or approval of marketing applications within the country.

Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drugs for which we may obtain regulatory approval. In the United States and in other countries, sales of any drugs for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug may be separate from the process for setting the reimbursement rate that the payor will pay for the drug. Third-party payors may limit coverage to specific drugs on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Moreover, a payor's decision to provide coverage for a drug does not imply that an adequate reimbursement rate will be approved. Additionally, coverage and reimbursement for drugs can differ significantly from payor to payor. One third-party payor's decision to cover a particular drug does not ensure that other payors will also provide coverage for the drug, or will provide coverage at an adequate reimbursement rate. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of drugs and services, in addition to their safety and efficacy. To obtain coverage and reimbursement for any drug that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies to demonstrate the medical necessity and cost-effectiveness of our drug. These studies will be in addition to the studies required to obtain regulatory approvals. If third-party payors do not consider a drug to be cost-effective compared to other available therapies, they may not cover the drug after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its drugs at a profit.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic drugs for branded prescription drugs. By way of example, the PPACA contains provisions that may reduce the profitability of drugs, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for our drugs.

In the European community, governments influence the price of drugs through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those drugs to consumers. Some jurisdictions operate positive and negative list systems under which drugs may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical studies that compare the cost effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new drugs. In addition, in some countries, cross border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any drugs for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, the focus on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if we attain favorable coverage and reimbursement status for one or more drugs for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Sales and Marketing

Numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the U.S. Department of Health and Human Services, the U.S. Department of Justice, and similar foreign, state and local government authorities, regulate sales, promotion and other activities following drug approval. As described above, the FDA regulates all advertising and promotion activities for drugs under its jurisdiction both prior to and after approval. Only those claims relating to safety and efficacy that the FDA has approved may be used in labeling. Physicians may prescribe legally available drugs for uses that are not described in the drug's labeling and that differ from those we tested and the FDA approved. Such off-label uses are common across medical specialties and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. If we do not comply with applicable FDA requirements, we may face adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA. Promotion of off-label uses of drugs can also implicate the false claims laws described below.

In the United States sales, marketing and scientific/educational programs must also comply with various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. Due to the breadth of the statutory provisions, limited statutory exceptions and regulatory safe harbors, and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that our practices might be challenged under anti-kickback or similar laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the PPACA among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes to clarify that a person or entity does not need to have

actual knowledge of this statute or specific intent to violate it. In addition, PPACA clarifies that the government may assert that a claim that includes items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims statutes. False claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to third-party payors (including Medicare and Medicaid) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our drugs may be subject to scrutiny under these laws. Violations of fraud and abuse laws may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also can be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called "responsible corporate officer" doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing.

Given the significant penalties and fines that can be imposed on companies and individuals if convicted, allegations of such violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals can bring similar actions. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing attention being given to them by law enforcement authorities. Other healthcare laws that may affect our ability to operate include 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, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information; analogous state laws governing the privacy and security of health information, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, and the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics, and medical supplies to report annually to the U.S. Department of Health and Human Services information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members. Further, there are an increasing number of state laws that require manufacturers to make reports to states on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions are imposed on the promotion and marketing of drugs in the European Union and other countries. Even in those countries where we may not be directly responsible for the promotion and marketing of our drugs, if our potential international distribution partners engage in inappropriate activity it can have adverse implications for us.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party, or candidate for the purpose of influencing any act or decision of the foreign entity 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 accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from government contracts.

Employees

As of February 20, 2019, we employed 248 people. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees and management considers relations with our employees to be good.

Corporate Information

We incorporated in Delaware in December 2014. Our principal offices are in Boston, Massachusetts. We make available, free of charge, on our website, *www.akceatx.com*, our reports on Forms 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that we include on or link to our website is not a part of this report or any registration statement that incorporates this report by reference. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is *www.sec.gov*.

Executive Officers of Akcea

The following sets forth certain information regarding our executive officers as of February 20, 2019:

Name	Age	Position
Paula Soteropoulos	51	Chief Executive Officer
Sarah Boyce	47	President
Michael MacLean	53	Chief Financial Officer
Jeffrey M. Goldberg	46	Chief Operating Officer
Louis St. L. O'Dea, MB BCh BAO, FRCP(C)	68	Chief Medical Officer

PAULA SOTEROPOLOUS

Chief Executive Officer

Ms. Soteropoulos joined Akcea as Chief Executive Officer and as a member of our board of directors in January 2015. Prior to joining Akcea, Ms. Soteropoulos was a member of the executive leadership team of Moderna Therapeutics Inc., now a public biotechnology company, serving as the Cardiometabolic Business Unit General Manager and Senior Vice President of Strategic Alliances from July 2013 to December 2014. Prior to Moderna, Ms. Soteropoulos spent 21 years at Genzyme Corporation in various leadership positions driving strategy, sales and marketing, business development, manufacturing process development, strategic capacity planning, and supply chain development. Since July 2013, Ms. Soteropoulos has served on the supervisory board of uniQure N.V., a public biotechnology company. Ms. Soteropoulos also serves on the advisory board of the Tufts University Chemical and Biological Engineering Department. Our board of directors believes that Ms. Soteropoulos is uniquely suited to serve on our board of directors because of her experience in the biotechnology industry and her daily insight into corporate matters as our Chief Executive Officer.

SARAH BOYCE

President

Ms. Boyce joined Akcea as a Board member and President in April 2018. Previously, she was the Chief Business Officer of Ionis Pharmaceuticals. In this role Ms. Boyce was responsible for leading investor relations and corporate communications, business development, alliance management, competitive intelligence and patient advocacy. She led the effort to establish a global agreement with Ionis and Novartis to develop and commercialize AKCEA APO(a)-L_{Rx} and AKCEA APOCIII-L_{Rx}. Ms. Boyce also served as Vice President, Head of International Business Strategy and Operations at Forest Laboratories, Inc. where she led the establishment and expansion of their international pharmaceutical and consumer health businesses. Prior to Forest, she served as a global business leader at Alexion and Novartis. Sarah Boyce is an experienced life sciences industry leader who has built out and overseen divisions and global commercial operations for a range of innovative therapies including Soliris®, Gleevec® and Tasigna®.

MICHAEL MACLEAN

Chief Financial Officer

Mr. MacLean has served as Chief Financial Officer of Akcea since September 2017. Prior to joining Akcea, from September 2015 to September 2017, Mr. MacLean was Chief Financial Officer and Executive Vice President for PureTech Health, an advanced, clinical-stage, public biopharmaceutical company focusing on diseases caused by dysfunctions in the nervous, gastrointestinal and immune systems. Previously, Mr. MacLean served as Senior Vice President of Finance and Chief Accounting Officer of Biogen Inc. where he led the Company's worldwide finance organization.

JEFFREY M. GOLDBERG

Chief Operating Officer

Mr. Goldberg joined Akcea as Chief Operating Officer in January 2015. Prior to joining Akcea, from December 2012 to September 2014, Mr. Goldberg was a member of the executive leadership team at Proteostasis Therapeutics, Inc., now a public biotechnology company focusing on neurology and orphan diseases, where he served as Vice President of Business Operations. Prior to that, Mr. Goldberg spent over 11 years in positions of increasing responsibility with Genzyme and Sanofi S.A., most recently as Associate Vice President, Project Head, within Sanofi Oncology.

LOUIS ST. L. O'DEA

Chief Medical Officer

Dr. O'Dea joined Akcea as Chief Medical Officer in January 2016. Prior to joining Akcea, Dr. O'Dea was Chief Medical Officer at Oxford Immunotec Global PLC, now a public diagnostics company, from June 2014 to January 2016, overseeing medical affairs and clinical development. Prior to Oxford, Dr. O'Dea was Chief Medical Officer and Head of Regulatory Affairs at Moderna from January 2012 to June 2014. Before Moderna, Dr. O'Dea held positions including Chief Medical Officer at Radius Health, Inc., a public biopharmaceuticals company, an academic position at McGill University, and worldwide Head of Clinical Development for Endocrine and Metabolic products at Serono.

ITEM 1A. RISK FACTORS

Investing in our securities involves a high degree of risk. You should consider carefully the following information about the risks described below, together with the other information contained in this Report and in our other public filings in evaluating our business. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. 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 currently believe to be immaterial may also adversely affect our business.

Risks Related to Our Financial Condition and Need for Additional Capital

We have a limited operating history and may never become profitable.

Ionis Pharmaceuticals, Inc., or Ionis, incorporated us as a Delaware corporation in December 2014, and we have operated as an affiliate of Ionis since that time. As such, we have limited experience as a company, and no experience operating independently from Ionis, and have not yet demonstrated that we can successfully overcome many of the risks and uncertainties frequently encountered in new and rapidly evolving fields, particularly the biotechnology and pharmaceutical fields.

As a company, we have limited experience commercializing products. Our ability to generate substantial revenue and achieve profitability depends on our ability, alone or with strategic partners, to successfully develop our drugs, obtain the regulatory approvals necessary to commercialize our drugs, including WAYLIVRA™ (volanesorsen), AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, and continue the commercialization of TEGSEDI ™ (inotersen). Although we received our first revenue from product sales in the fourth quarter of 2018, if we are not successful in growing revenue and controlling costs, we will not achieve profitable operations or positive cash flow, and even if we achieve profitability in the future, we may not sustain profitability in subsequent periods. Our ability to generate revenue sufficient to achieve profitability from product sales depends heavily on our and our current and future strategic partners' success in:

- completing clinical development of WAYLIVRA for additional indications and nonclinical and clinical development of AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx};
- seeking and obtaining regulatory and marketing authorization for our drugs, including TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx} and our other drugs in development;
- managing supply and manufacturing relationships with third parties that can provide the amount and quality of products and services we need to continue to commercialize TEGSEDI and to develop and, if approved, commercialize WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development;
- launching and commercializing WAYLIVRA, AKCEA-ANGPTL3-L_{Rx} and AKCEA-TTR-L_{Rx} and continuing the commercialization of TEGSEDI by managing a sales, marketing and distribution infrastructure;
- launching and co-commercializing AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} through our collaboration with Novartis Pharma AG, or Novartis, under terms that we may negotiate with Novartis in the future;
- educating physicians about our target patient populations, including the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adult patients in the United States, stage 1 or stage 2 polyneuropathy in adult patients with hereditary TTR Amyloidosis, or hATTR, in the EU or Canada, patients with familial chylomicronemia syndrome, or FCS, and patients with familial partial lipodystrophy, or FPL;

- obtaining market acceptance of TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development as viable treatment options;
- obtaining and maintaining adequate coverage and reimbursement from third-party payors for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development;
- addressing any competing technological and market developments;
- negotiating favorable terms in any partnership, licensing or other arrangements into which we may enter;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, product trademarks and know-how;
- developing and commercializing WAYLIVRA, AKCEA-ANGPTL3-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development and continuing the commercialization of TEGSEDI without infringing others' intellectual property rights; and
- attracting, hiring and retaining qualified personnel.

We may not successfully develop our products or generate product revenue sufficient to cover operating expenses or become profitable. If we cannot achieve or maintain profitability, it would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. If the market price of our common stock declined, you could lose all or part of your investment.

We have incurred losses since our inception.

Because drug development requires substantial lead-time and funding prior to commercialization, we have incurred expenses while generating limited revenue from our operating activities since our formation. Our net losses were $225.8 million and $121.6 million for the years ended December 31, 2018 and December 31, 2017 (as revised), respectively. As of December 31, 2018, we had an accumulated deficit of approximately $522.0 million. Most of the losses resulted from costs incurred in connection with our development programs and from general and administrative costs associated with our operations. We expect to incur additional operating losses for the foreseeable future, and these losses may increase if we cannot generate substantial revenue.

We will require substantial additional funding to achieve our goals. If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All of our drugs are undergoing clinical studies. All of our drug programs, except TEGSEDI in the United States, EU, and Canada, will require additional nonclinical and/or clinical testing and/or marketing authorization prior to commercialization. We will need to spend significant additional resources to conduct these activities. Our expenses could increase beyond expectations if the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities require us to perform clinical studies and other studies in addition to those that we currently anticipate. As of December 31, 2018, we had cash, cash equivalents and investments equal to $252.6 million. Our operating expenses were $295.7 million and $163.9 million for the ended December 31, 2018 and December 31, 2017, respectively.

Prior to our IPO, we funded our operating activities through a $100.0 million cash contribution we received from Ionis in 2015, $75.0 million that we received from initiating our collaboration with Novartis and $106.0 million in drawdowns under our line of credit with Ionis. The line of credit converted to our common stock when we closed our IPO. We no longer have access to the line of credit following the closing of our IPO and we do not have any firm commitment from Ionis to fund our cash flow deficits or provide other direct or indirect financial assistance to us. Additionally, in July 2017 we received $182.3 million in net proceeds from our IPO including $25.0 million that Ionis invested in our IPO and the Novartis concurrent private placement of $50.0 million. In April 2018, we received $200.0 million from the common stock we issued in connection with the licensing transaction with Ionis discussed in Note 7, *License Agreements and Services Agreement with Ionis*, to our consolidated financial statements included in this Form 10-K. We expect that we will need to raise additional funding to continue developing the drugs in our pipeline and to seek regulatory approval for and to commercialize TEGSEDI, WAYLIVRA and other drugs in our pipeline.

We have received marketing authorization approval for TEGSEDI from the FDA for the treatment of the polyneuropathy of hATTR in adult patients in the United States, from the European Commission, or EC, and from Health Canada for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR, and we will continue to incur significant costs commercializing TEGSEDI. Even if we obtain marketing authorizations to sell WAYLIVRA, AKCEA-APO(a)-L_{Rx} or AKCEA-TTR-L_{Rx}, we will incur

significant costs to commercialize the approved product. To date, only one of our product(s), TEGSEDI, has commercially launched, and even if we generate substantial revenue from the sale of approved products, we may not become profitable and would need to obtain additional funding to continue operations.

Risks Related to Clinical Development, Regulatory Review and Approval of Our Drugs

If the results of clinical testing indicate that any of our drugs are not suitable for commercial use, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense drugs are a relatively new approach to therapeutics. If we cannot demonstrate that our drugs are safe and effective for human use in the intended indication, we may need to abandon one or more of our drug development programs.

If any of our drugs in clinical studies, including WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, do not show sufficient safety and efficacy in patients with the targeted indication, it would negatively affect our development and commercialization goals for the drug and we would have expended significant resources with little or no benefit to us.

Even if our drugs are successful in preclinical and earlier-stage clinical studies, the drugs may not be successful in later-stage clinical studies.

Successful results in preclinical or initial clinical studies, including the results of earlier studies for our drugs in development, may not predict the results of subsequent clinical studies, including the Phase 3 study of WAYLIVRA for the treatment of FPL and the Phase 3 study of AKCEA-APO(a)-L_{Rx} in patients with established cardiovascular disease and elevated levels of lipoprotein(a). There are a number of factors that could cause a clinical study to fail or be delayed, including:

- the clinical study may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical study due to adverse side effects of a drug on people in the study;
- we or our partners may decide, or regulators may require us, to conduct additional preclinical testing or clinical studies;
- we or our partners may not identify, recruit and train suitable clinical investigators at a sufficient number of study sites;
- the institutional review board for a prospective site might withhold or delay its approval for the study;
- enrollment in our clinical studies may be slower than we anticipate;
- patients who enroll in the clinical study may later drop out due to adverse events, a perception they are not benefiting from participating in the study, fatigue with the clinical study process or personal issues;
- a clinical study site may deviate from the protocol for the study;
- the cost of our clinical studies may be greater than we anticipate;
- we or our partners may require additional capital to fund the clinical study;
- our partners may decide not to exercise any existing options to license and conduct additional clinical studies for our drugs; and
- the supply or quality of our drugs or other materials necessary to conduct the clinical studies may be insufficient, inadequate or delayed.

In addition, WAYLIVRA and AKCEA-APOCIII-L_{Rx} have the same mechanism of action, TEGSEDI and AKCEA-TTR-L_{Rx}, also have the same mechanism of action and all of our current drugs, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, are chemically similar to each other and the drugs Ionis and other companies are developing separately. As a result, a safety observation we, Ionis or other companies encounter with one of our or their drugs could have or be perceived by a regulatory authority to have an impact on a different drug we are developing. This could cause the FDA and other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our drugs or

increase our costs. For example, the FDA or other regulatory agencies could request, among other things, any of the following regarding one of our drugs: additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. Similarly, we have an ongoing Phase 3 study of WAYLIVRA in patients with FPL, an ongoing open label extension study of WAYLIVRA in patients with FCS and an open label extension study of TEGSEDI in patients with hATTR, and an early access program, or EAP, for both WAYLIVRA and TEGSEDI. Adverse events or results from these studies or the EAPs could negatively impact our pending or future marketing approval applications for WAYLIVRA and TEGSEDI in patients with FCS or hATTR amyloidosis or the commercial opportunity for WAYLIVRA or TEGSEDI. In August 2018 we received a Complete Response Letter, or CRL, from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Notice of Noncompliance withdrawal letter, or Non-W, from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any revenue or profit from the sale of WAYLIVRA. The regulatory authorities and Europe could have a similar response to the pending marketing authorization application. Any failure or delay in the clinical studies for any of our drugs in development could reduce the commercial potential or viability of our drugs.

We may not have appropriately designed the planned and ongoing clinical studies for WAYLIVRA, AKCEA-APO(a)-L$_{Rx}$, AKCEA-TTR-L$_{Rx}$ and our other drugs in development to support submission of a marketing application to the FDA and foreign regulatory authorities or demonstrate safety or efficacy at the level required by the FDA and foreign regulatory authorities for product approval.

We completed a Phase 3 clinical program for WAYLIVRA for the treatment of FCS in 2018 and are conducting or plan to conduct additional clinical studies for WAYLIVRA in patients with FPL, as well as for AKCEA-TTR-L$_{Rx,}$ AKCEA-APO(a)-L$_{Rx}$, AKCEA-ANGPTL3-L$_{Rx}$ and AKCEA-APOCIII-L$_{Rx}$.

Even if we achieve positive results on the endpoints for these clinical studies or any future clinical studies, the FDA or foreign regulatory authorities may believe the clinical studies do not show the appropriate balance of safety and efficacy in the indication being sought or may interpret the data differently than we do, and deem the results insufficient to demonstrate the appropriate balance of safety and efficacy at the level required for product approval. For example, in August 2018 we received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to the FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any revenue or profit from the sale of WAYLIVRA. The CHMP of the EMA has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway, however, the EC may decide not to adopt the CHMP's positive opinion. These risks are more likely to occur since we are developing our drugs against therapeutic targets or to treat diseases in which there is little or no clinical experience. In addition, these risks may be more likely to occur for WAYLIVRA since there were some patients in the Phase 3 program that experienced serious platelet events (grade 4 thrombocytopenia), a condition in which the patient has very low platelet levels, and additional patients experienced other adverse events in the program, including patients who discontinued participation in the APPROACH study due to platelet count declines. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent.

We may make modifications to the clinical study protocols or designs of our ongoing clinical studies that delay enrollment or completion of such clinical studies and could delay regulatory approval of WAYLIVRA and our other drugs in development. Any failure to obtain approval for WAYLIVRA, AKCEA-APO(a)-L$_{Rx,}$ AKCEA-TTR-L$_{Rx}$ and our other drugs in development on the timeline that we currently anticipate, or at all, would have a material and adverse impact on our business, prospects, financial condition and results of operations and could cause our stock price to decline.

Clinical studies for WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} or our other drugs may not demonstrate safety or efficacy at the level required by the FDA and foreign regulatory authorities for product approval.

The EMA is currently reviewing our application for regulatory approval for WAYLIVRA. The CHMP of the EMA has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed FCS who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway, however, the EC may decide not to adopt the CHMP's positive opinion. We and Ionis are conducting or intend to conduct clinical studies for AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}.

Even if positive results on the endpoints for the clinical studies are achieved, the FDA or foreign regulatory authorities may believe the clinical studies do not show the appropriate balance of safety and efficacy in the indication being sought or may interpret the data differently than we do, and may deem the results insufficient to demonstrate the appropriate balance of safety and efficacy at the level required for product approval. For example, in August 2018 we received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any revenue or profit from the sale of WAYLIVRA. The regulatory authorities in Europe could have a similar response to the pending marketing authorization application. As an additional example, the foreign regulatory authorities could claim that we have not tested WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx} in a sufficient number of patients to demonstrate that the drug is safe and effective in patients with other indications to support an application for marketing authorization for the applicable indication. In such a case, we may need to conduct additional clinical studies before obtaining marketing authorization, which would be expensive and delay the development and commercialization of the drug.

Any failure to obtain approvals for WAYLIVRA in other important markets outside of the United States and Canada, including the EU, on the timeline that we currently anticipate, or at all, would have a material and adverse impact on our business, prospects, financial condition and results of operations and could cause our stock price to decline.

If we or our partners fail to obtain regulatory approval for our drugs, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, or additional approvals for TEGSEDI, we or our partners cannot sell them in the applicable markets.

We cannot guarantee that any of our drugs, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, will be safe and effective, or will be approved or receive additional approvals for commercialization. We and our partners must conduct time-consuming, extensive and costly clinical studies to demonstrate the safety and efficacy of each of our drugs, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, before they can be approved, or receive additional approvals, for sale. We and our partners must conduct these studies in compliance with FDA regulations and with comparable regulations in other countries.

We or our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. It is possible that regulatory authorities will not approve TEGSEDI in additional markets or any of our other drugs, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, for marketing. If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our drugs, including WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, the authority will not approve the specific drug or will require additional studies, which can be time consuming and expensive and which will delay or harm our ability to successfully commercialize the drug. For example, in August 2018 we received a CRL from the FDA regarding the new drug application for WAYLIVRA in which the FDA determined that the safety concerns identified with WAYLIVRA in our clinical development program outweighed the expected benefits of triglyceride lowering in patients with FCS. We also received a Non-W from Health Canada for WAYLIVRA in November 2018. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA. As a result, we will need to submit additional data to FDA and may need to conduct additional clinical studies before obtaining marketing authorization, which in turn could delay or prevent us from generating any revenue or profit from the sale of WAYLIVRA. The regulatory authority in Europe could have a similar response to the pending marketing authorization.

The FDA or other comparable foreign regulatory authorities can delay, limit or deny approval of a drug for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical studies;
- we or our partners may be unable to demonstrate to the satisfaction of the FDA or other regulatory authorities that a drug is safe and effective for any indication;
- such authorities may not accept clinical data from studies conducted at clinical facilities that have deficient clinical practices or that are in countries where the standard of care is potentially different from the United States;
- we or our partners may be unable to demonstrate that our drug's clinical and other benefits outweigh its safety risks to support approval;
- such authorities may disagree with the interpretation of data from preclinical or clinical studies;
- such authorities may find deficiencies in the manufacturing processes or facilities of third-party manufacturers who manufacture clinical and commercial supplies for our drugs; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

Failure to successfully develop WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, or to receive marketing authorization for these drugs in important markets or delays in these authorizations would prevent or delay the commercial launch of the drug, and, as a result, would negatively affect our ability to generate revenue.

We may not be able to benefit from orphan drug designation for WAYLIVRA, TEGSEDI or any of our other drugs.

The FDA and EMA have granted orphan drug designation to TEGSEDI and to WAYLIVRA for the treatment of patients with FCS. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. The FDA, however, refused to grant our request for orphan drug designation for WAYLIVRA for the treatment of patients with FPL in the United States in 2017.

In the United States, under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is 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. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods.

Even if approval is obtained on a drug that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable drug to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same drug in a safer or more effective form or that makes a major contribution to patient care.

Even if we maintain orphan drug exclusivity for TEGSEDI or WAYLIVRA for the treatment of patients with FCS or obtain orphan drug exclusivity for our other drugs, the exclusivity may not effectively protect the drug from competition because regulatory authorities still may authorize different drugs for the same condition.

We may expend our limited resources to pursue a particular drug or indication and fail to capitalize on drugs or indications that may be more profitable or for which there is a greater likelihood of success.

We will continue to dedicate a substantial amount of our resources to commercialize TEGSEDI and support the continued development of AKCEA-TTR-L_{Rx}. In addition, we may dedicate a substantial amount of our resources to develop and seek regulatory approval for WAYLIVRA to treat patients with FCS and FPL. As a result, we may forego or delay pursuit of opportunities with our other drugs or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and drugs for specific indications may not yield any commercially viable drugs.

Our drugs, including TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, could be subject to regulatory limitations following approval.

Following approval of a drug, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of drug products. Promotional communications regarding prescription drugs must be consistent with the information in the product's approved labeling. We and our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our drug products, including TEGSEDI, and if approved, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development.

The FDA and foreign regulatory authorities can impose significant restrictions on an approved drug product through the product label and on advertising, promotional and distribution activities. For example:

- In the United States, TEGSEDI's label contains a boxed warning for thrombocytopenia and glomerulonephritis,
- TEGSEDI requires periodic blood and urine monitoring, and
- in the United States TEGSEDI is available only through a Risk Evaluation and Mitigation Strategy, or REMS, program.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. If the results of such post-marketing studies are not satisfactory, the FDA or a foreign regulatory authority may withdraw marketing authorization or may condition continued marketing on commitments from us or our partners that may be expensive and/or time consuming to fulfill.

In addition, if we or others identify side effects after any of our drug products are on the market, if manufacturing problems occur subsequent to regulatory approval, or if we, our manufacturers or our partners fail to comply with regulatory requirements, we or our partners could be subject to:

- changes to the product label;
- restrictions on the marketing of a product;
- restrictions on product distribution;
- restrictions on such products' manufacturing processes;
- requirements to conduct post-marketing clinical studies;
- 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 revenue;
- suspension or withdrawal of regulatory approvals;
- refusal to permit the import or export of our products;
- product seizure;
- injunctions;
- restrictions on our ability to conduct clinical studies, including full or partial clinical holds on ongoing or planned clinical studies; or
- imposition of civil or criminal penalties.

Any one or a combination of these events could prevent us from achieving or maintaining market acceptance of the affected drug product or could substantially increase the costs and expenses of commercializing such drug product, which in turn could delay or prevent us from generating any revenue or profit from the sale of the drug product.

The development and commercialization of TEGSEDI and WAYLIVRA may place strain on our management team's time and attention and may divert our management team's attention from our other existing products.

Although we have personnel with experience commercializing drugs, we ourselves have limited experience commercializing products. We commercially launched TEGSEDI during the fourth quarter of 2018 and, if regulatory approval is obtained, we plan to commercially launch WAYLIVRA during 2019. The commercial launch of TEGSEDI will continue to and, if approved, the commercial launch of WAYLIVRA will, require significant efforts and the devotion of substantial resources, as we finalize regulatory submissions, manage the manufacturing of sufficient quantities of product to support long-term commercial sales and integrate, optimize or maintain, as applicable, the global sales, marketing, medical, for each of WAYLIVRA and TEGSEDI, and patient support infrastructure, which may place pressure on the management team's time and attention. These efforts may also divert the attention of the management team from our other business operations, such as the development or commercialization of our other pipeline products, including AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-$L_{Rx,}$ AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}. As a result, our business, results of operations, financial condition and prospects for future growth could be adversely impacted and the market price of our common stock may decline.

Risks Related to Commercialization of Our Drugs

If we cannot effectively manage our marketing and sales capabilities or enter into agreements with third parties to market and sell our drug products, we may not generate product revenue.

We commercially launched TEGSEDI in the fourth quarter of 2018 and, if approved, plan to commercialize WAYLIVRA. To successfully commercialize TEGSEDI and WAYLIVRA, we must effectively manage our marketing, sales and distribution capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. To commercialize WAYLIVRA in the initial indications we plan to pursue and to continue the commercialization of TEGSEDI, we will need to optimize and maintain specialty sales forces in the global regions where we currently market or expect to market TEGSEDI and WAYLIVRA, supported by case managers, reimbursement specialists, partnerships with specialty pharmacies, injection training, routine blood and urine monitoring and a medical affairs team. We may seek to further penetrate markets by expanding our sales forces or through strategic partnerships with other pharmaceutical or biotechnology companies or third-party sales organizations.

Even though certain members of our management team and other employees have significant experience commercializing drug products, as a company we have limited experience marketing, selling or distributing drug products, and there are significant risks involved in building and managing a commercial infrastructure. It is expensive and time consuming for us to maintain our own sales forces and related compliance protocols to market TEGSEDI and it will be increasingly expensive and time consuming as we commercially launch additional drug products, if approved. We may never successfully optimize or manage this capability and any failure could delay or preclude the commercial launch of WAYLIVRA or adversely affect TEGSEDI sales. We and our partners, if any, will have to compete with other companies to recruit, hire, train, manage and retain marketing and sales personnel. As a result of our receipt of a CRL from the FDA regarding the new drug application for WAYLIVRA, on September 6, 2018, we enacted a plan to reorganize our workforce to better align with the immediate needs of our business. In connection with this reorganization plan, we reduced our workforce by approximately 12%. If WAYLIVRA is subsequently approved in the United States, we will again need to increase our operations and expand our use of third-party contractors.

We have incurred expenses launching TEGSEDI in the EU, Canada and the U.S. and integrating and managing the marketing and sales infrastructure. If regulatory requirements or other factors cause the commercialization of TEGSEDI to be less successful than expected in important markets, we would incur additional expenses for having invested in these capabilities prior to realizing any significant revenue from sales of TEGSEDI. Our sales force and marketing teams may not successfully commercialize TEGSEDI.

We will incur expenses prior to the launch of WAYLIVRA to integrate and manage the marketing and sales infrastructure. If regulatory requirements or other factors cause a delay in the commercial launch of WAYLIVRA, we would incur additional expenses for having invested in these capabilities earlier than required and prior to realizing any revenue from sales of WAYLIVRA. Our sales force and marketing teams may not successfully commercialize WAYLIVRA.

To the extent we decide to rely on third parties to commercialize TEGSEDI or WAYLIVRA in a particular geographic market, we may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. For example, in August 2018, we granted PTC Therapeutics International Limited, or PTC Therapeutics, the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries, and will continue to rely on PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in those geographic markets. In addition, in August 2018 we entered into an agreement with Accredo Health Group, Inc., or Accredo, a subsidiary of Express Scripts, to be our specialty pharmacy partner for distribution of TEGSEDI in the U.S. Further, we have less control over the sales efforts of other third parties, including PTC Therapeutics and Accredo, involved in commercializing TEGSEDI or WAYLIVRA.

If we cannot effectively build and manage our distribution, medical affairs, market access, marketing and sales infrastructure, or find a suitable third party to perform such functions, the sales of TEGSEDI and commercial launch of WAYLIVRA may be adversely affected, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

If we are unable to rely on third-party specialty channels to distribute our drugs to patients we may be unable to generate adequate revenue

We and our strategic partners have contracted with, rely on and will continue to rely on third-party specialty pharmacies to distribute our drugs to patients. A specialty pharmacy is a pharmacy that specializes in dispensing medications for complex or chronic conditions, a process that requires a high level of patient education and ongoing management. Our management team will need to devote a significant amount of its attention to optimizing and managing this distribution network. If we cannot effectively optimize and manage this distribution process, the commercial launch of WAYLIVRA, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx} and the sales of TEGSEDI will be adversely affected.

In addition, the use of specialty pharmacies involves certain risks, including, but not limited to, risks that these organizations will:

- not provide us with accurate or timely information regarding their inventories, the number of patients who are using our drugs or complaints regarding our drugs;
- not effectively sell or support TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} or our other drugs;
- reduce or discontinue their efforts to sell or support TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} or our other drugs;
- not devote the resources necessary to sell TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} or our other drugs in the volumes and within the time frames that we expect;
- not satisfy financial obligations to us or others; or
- cease operations.

Any such events may result in decreased sales and lower revenue, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

If the market does not accept our drugs, including TEGSEDI, WAYLIVRA, AKCEA-TTR-L_{Rx} and our other drugs in development, we are not likely to generate substantial product revenue or become profitable.

Even though we have obtained marketing authorization approval from the FDA, the EC and Health Canada for TEGSEDI, and if we or our strategic partners obtain a marketing authorization for WAYLIVRA, AKCEA-TTR-L_{Rx} and our other drugs in development, our success will depend upon the medical community, patients and third-party payors accepting our drugs as medically useful, cost-effective, safe and convenient. Even if the FDA or foreign regulatory authorities authorize our drugs for commercialization, doctors may not prescribe our drugs to treat patients. We and our partners may not successfully commercialize additional drugs.

Additionally, in many of the markets where we or our partners may sell our drugs in the future, if we cannot agree with the government or other third-party payors regarding the price we can charge for our drugs, then we may not be able to sell our drugs in that market. Similarly, cost control initiatives by governments or third-party payors could decrease the price received for our drugs or increase patient coinsurance to a level that makes the continued commercializing of TEGSEDI and the commercializing of WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development economically unviable.

The degree of market acceptance for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development depends upon a number of factors, including the:

- receipt and scope of marketing authorizations;
- establishment and demonstration in the medical and patient community of the efficacy and safety of our drugs and their potential advantages over competing products;
- cost and effectiveness of our drugs compared to other available therapies;
- patient convenience of the dosing regimen for our drugs; and
- reimbursement by government and third-party payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors or the medical community in general may not accept and/or use any drugs that we may develop.

For example, the product label for TEGSEDI in the United States has a boxed warning for thrombocytopenia and glomerulonephritis, requires periodic blood and urine monitoring, and TEGSEDI has a Risk Evaluation and Mitigation Strategy, or REMS, program. Our main competition in the U.S. market for TEGSEDI is ONPATTRO (patisiran), marketed by Alnylam Pharmaceuticals, Inc. Although ONPATTRO requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning or REMS. Additionally, in the clinical studies with WAYLIVRA, declines in platelet counts were observed in many patients and some patients discontinued the study because of platelet declines. Therefore, we expect the product label for WAYLIVRA will require periodic blood monitoring. In each case, these label requirements could negatively affect our ability to attract and retain patients for these drugs. We believe that the enhanced monitoring we have implemented to support early detection and management of these issues can help manage these safety issues so that patients can continue treatment. Since implementation of the enhanced monitoring, serious platelet events have been infrequent. While we believe we can better maintain patients on TEGSEDI and WAYLIVRA through our patient-centric commercial approach where we plan to have greater involvement with physicians and patients, if we cannot effectively maintain patients on TEGSEDI and WAYLIVRA, we may not be able to generate substantial revenue from TEGSEDI and WAYLIVRA sales.

The patient populations suffering from FCS and FPL are small and have not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of these diseases and diagnosis is not improved, our revenue and ability to achieve profitability from WAYLIVRA may be adversely affected.

We estimate there are 3,000 to 5,000 FCS patients and an additional 3,000 to 5,000 FPL patients globally. Our estimates of the sizes of the patient populations are based on published studies as well as internal analyses. If the results of these studies or our analyses of them do not accurately reflect the number of patients with FCS and FPL, our assessment of the market potential for WAYLIVRA may be inaccurate, making it difficult or impossible for us to meet our revenue goals, or to obtain and maintain profitability. In addition, as is the case with most orphan diseases, if we cannot successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability.

In addition, since the patient populations for FCS and FPL are small, the per-patient drug pricing must be priced appropriately in order to recover our development and manufacturing costs, fund adequate patient support programs and achieve profitability. For these initial indications, we may not maintain or obtain sufficient sales volume at a price that justifies our product development efforts and our sales and marketing and manufacturing expenses.

The patient population suffering from hATTR amyloidosis is small and has not been established with precision. If the actual number of patients is smaller than we estimate, or if we cannot raise awareness of the disease and diagnosis is not improved, our revenue and ability to achieve profitability from either TEGSEDI or AKCEA-TTR-L_{Rx} may be adversely affected.

Our estimate of the sizes of the patient populations are based on published studies as well as internal analyses. If the results of these studies or our analyses of them do not accurately reflect the number of patients with hATTR amyloidosis, our assessment of the market potential for either TEGSEDI or AKCEA-TTR-L_{Rx} may be inaccurate, making it difficult or impossible for us to meet our revenue goals, or to obtain and maintain profitability. In addition, as is the case with most orphan diseases, if we cannot successfully raise awareness of these diseases and improve diagnosis, it will be more difficult or impossible to achieve profitability. For these initial indications, we may not maintain or obtain sufficient sales volume at a price that justifies our product development efforts and our sales and marketing and manufacturing expenses.

If we or our partners fail to compete effectively, WAYLIVRA, TEGSEDI and our other drugs in development will not contribute significant revenue.

Our competitors engage in drug discovery throughout the world, are numerous and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Our competitors may succeed in developing drugs that are:

- safer than our drugs;
- more effective than our drugs;
- priced lower than our drugs;
- reimbursed more favorably by government and other third-party payors than our drugs; or
- more convenient to use than our drugs.

These competitive developments could make our drugs, including WAYLIVRA, TEGSEDI, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, obsolete or non-competitive. Further, all of our drugs are delivered by injection, which may render them less attractive to patients than non-injectable products offered by our current or future competitors.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical studies, in obtaining FDA and other regulatory authorizations and in commercializing pharmaceutical products. Accordingly, our competitors may succeed in obtaining regulatory authorization for products earlier than we do. Marketing and sales capability is another factor relevant to the competitive position of our drugs, and many of our competitors will have greater marketing and sales capabilities than our capabilities.

There are several pharmaceutical and biotechnology companies engaged in the development or commercialization of products against targets that are also targets of drugs in our development pipeline. For example, if approved, WAYLIVRA could face competition from drugs like metreleptin and gemcabene. Metreleptin, produced by Novelion Therapeutics, Inc., is currently approved in the U.S. and E.U. for use in generalized lipodystrophy patients. WAYLIVRA may also compete with gemcabene, an oral small molecule that reduces apoC-III, that Gemphire Therapeutics, Inc. is developing to treat patients with triglycerides above 500 mg/dL.

As an additional example, TEGSEDI could face competition from drugs like ONPATTRO, marketed by Alnylam for hATTR amyloidosis with polyneuropathy in the U.S. and E.U., tafamidis, available in the E.U. for stage 1 hATTR amyloidosis with polyneuropathy and under review in the U.S. for ATTR with cardiomyopathy, and AG10, which is being developed by Eidos for patients with ATTR with cardiomyopathy. For example, ONPATTRO is approved in the United States and Europe for a similar and broader indication as TEGSEDI. AG10, which recently completed its Phase 2 dose-finding study, is an orally administered TTR tetramer stabilizer for ATTR amyloidosis. If WAYLIVRA, TEGSEDI or the other drugs in our pipeline cannot compete effectively with these and other products with common or similar indications to the drugs in our pipeline, we may not be able to generate substantial revenue from our product sales.

If government or other third-party payors fail to provide adequate coverage and payment rates for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development, our revenue and prospects for profitability will be limited.

In both domestic and foreign markets, sales of our future products will depend in part upon the availability of coverage and reimbursement from third-party payors. The majority of patients in the United States who would fit within our target patient populations for our drugs have their healthcare supported by a combination of Medicare coverage, other government health programs such as Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be enough to make our drugs affordable. Accordingly, TEGSEDI and, if approved, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, will face competition from other therapies and drugs for limited financial resources. We may need to conduct post-marketing studies to demonstrate the cost-effectiveness of any future products to satisfy third-party payors. These studies might require us to commit a significant amount of management time and financial and other resources. Third-party payors may never consider our future products as cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. For example, in the United States, recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries and proposed federal legislation designed to, among other things, reform government program reimbursement methodologies for drug products and bring more transparency to drug pricing. Third-party coverage and reimbursement for our products or drugs may not be available or adequate in either the United States or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If we are found in violation of federal or state "fraud and abuse" laws or other healthcare laws and regulations, we may be required to pay a penalty and/or be suspended from participation in federal or state healthcare programs, which may adversely affect our business, financial condition and results of operation.

We may be subject to various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws, among other things, make it illegal for a prescription drug manufacturer to pay, or offer to pay, a healthcare provider to refer, purchase or prescribe a particular drug. Due to the breadth of the statutory and regulatory provisions, it is possible that government authorities and others might challenge our practices under anti-kickback or other fraud and abuse laws. Moreover, recent healthcare reform legislation has strengthened these laws. In addition, false claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to government third-party payors, including Medicare and Medicaid claims for reimbursed drugs that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our products may be subject to scrutiny under these laws. If we violated fraud and abuse laws, we could face a combination of:

- criminal and civil sanctions, including fines and civil monetary penalties;
- the possibility of exclusion from federal healthcare programs, including Medicare and Medicaid; and
- corporate integrity agreements, which could impose rigorous operational and monitoring requirements on us.

Given the significant penalties and fines that the government can impose on companies and individuals if convicted, allegations of violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, and corporate integrity agreements. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals may bring similar actions under the False Claims Act. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing focus on these laws by law enforcement authorities. To the extent we have access to protected health information we could be subject to federal and state health information privacy and security laws, including without limitation, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic healthcare transactions and protects the security and privacy of protected health information. State health information privacy and security laws in certain circumstances are more stringent than HIPAA and many of the state laws differ from each other in significant ways and may not have the same effect, thus complicating compliance. Our failure to comply with applicable federal and state health information privacy and security laws could subject us to significant fines and multi-year corrective action plans. TEGSEDI commercially launched in the U.S. in the fourth quarter of 2018 and as such we are now required to report annually to Centers for Medicare and Medicaid Services certain information related to payments and other transfers of value we may provide to physicians and teaching hospitals. Further, an increasing number of state laws require manufacturers to make reports to states on pricing and marketing information. Many of these laws are unclear as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

Similar rigid restrictions related to anti-kickbacks and promoting and marketing medicinal products apply in the European Union and other countries. Authorities in these countries strictly enforce these restrictions. Even in those countries where we will not be directly responsible for promoting and marketing our products, inappropriate activity by any of our international commercialization partners we may have could harm us.

Risks Related to Dependence on Third Parties

We plan to substantially depend on our collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}.

We have granted Novartis an exclusive option to exclusively license each of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} pursuant to our strategic collaboration, option and license agreement with Novartis. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx}. We plan to substantially depend on Novartis to further develop and commercialize AKCEA-APO(a)-L_{Rx} and potentially AKCEA-APOCIII-L_{Rx}. We initiated this collaboration primarily to have Novartis:

- conduct the cardiovascular outcome studies that are likely to be required for approval of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-$L_{Rx;}$
- seek and obtain regulatory approvals for AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}; and
- globally commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}.

Since Novartis has exercised its option to license AKCEA-APO(a)-L_{Rx}, we will rely on Novartis to further develop, obtain regulatory approvals for, and commercialize it. In general, we cannot control the amount and timing of resources that Novartis devotes to our strategic collaboration. If Novartis fails to use commercially reasonable efforts to further develop, obtain regulatory approvals for, or commercialize AKCEA-APO(a)-L_{Rx}, or if Novartis' efforts are not effective, our business may be negatively affected. Novartis could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same diseases as we and Novartis plan to treat with AKCEA-APO(a)-L_{Rx}. Novartis could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing AKCEA-APO(a)-L_{Rx}, and Novartis is not required to inform us of such activities.

If Novartis exercises its option to license AKCEA-APOCIII-L_{Rx}, we would rely on Novartis to further develop, obtain regulatory approvals for, and commercialize it. In general, we cannot control the amount and timing of resources that Novartis devotes to our strategic collaboration. If Novartis fails to use commercially reasonable efforts to further develop, obtain regulatory approvals for, or commercialize AKCEA-APOCIII-L_{Rx}, or if Novartis' efforts are not effective, our business may be negatively affected. Novartis could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same disease as we and Novartis plan to treat with AKCEA-APOCIII-L_{Rx}. Novartis could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing AKCEA-APOCIII-L_{Rx} and Novartis is not required to inform us of such activities.

Our strategic collaboration with Novartis may not continue for various reasons. Novartis can terminate our agreement at any time and is under no obligation to exercise the options we granted them. If Novartis stops developing or commercializing AKCEA-APO(a)-L_{Rx}, or does not exercise its option to license AKCEA-APOCIII-$L_{Rx,}$ we will have to seek additional sources for funding and may have to delay or reduce our development and commercialization plans for these drugs.

In addition, following Novartis' exercise of its option to license AKCEA-APO(a)-L_{Rx} in February 2019, and if Novartis exercises its option to license AKCEA-APOCIII-L_{Rx}, Novartis will be responsible for the long-term supply of drug substance and finished drug product for the licensed drug.

Our strategic collaboration with Novartis may not result in the successful commercialization of AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}. If Novartis does not successfully develop, manufacture or commercialize AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx}, we may receive limited or no revenues for these drugs.

We plan to substantially depend on our collaboration with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries.

In August 2018, we granted PTC Therapeutics International Limited the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. We plan to substantially depend on PTC to commercialize these drugs in those geographic markets.

In general, we cannot control the amount and timing of resources that PTC devotes to our strategic collaboration. If PTC fails to use commercially reasonable efforts to obtain regulatory approvals for, or commercialize these drugs, or if PTC's efforts are not effective, our business may be negatively affected. PTC could pursue other technologies or develop other drugs either on its own or in collaboration with others to treat the same diseases as we and PTC plan to treat with TEGSEDI and WAYLIVRA. PTC could pursue these technologies and develop these other drugs at the same time as it is developing or commercializing TEGSEDI and WAYLIVRA, and PTC is not required to inform us of such activities.

Our strategic collaboration with PTC may not continue for various reasons. If PTC stops commercializing a drug, we will have to seek additional sources for funding and may have to delay or reduce our commercialization plans for TEGSEDI and WAYLIVRA in Latin America or certain Caribbean countries.

Our strategic collaboration with PTC may not result in the successful commercialization of TEGSEDI or WAYLIVRA in Latin America or certain Caribbean countries. If PTC does not successfully commercialize TEGSEDI or WAYLIVRA, we may receive limited revenue for TEGSEDI or no revenue for WAYLIVRA in Latin America or certain Caribbean countries.

AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx} may compete with WAYLIVRA, which could reduce our expected revenues for WAYLIVRA.

WAYLIVRA and AKCEA-APOCIII-L_{Rx} both inhibit the production of the same protein. We believe the enhancements we incorporated into AKCEA-APOCIII-L_{Rx} can provide greater patient convenience by allowing for significantly lower doses and less frequent administration compared to WAYLIVRA. As such, if Novartis exercises its option and successfully commercializes AKCEA-APOCIII-L_{Rx} while we are commercializing WAYLIVRA, to the extent physicians and patients elect to use AKCEA-APOCIII-L_{Rx} instead of WAYLIVRA, it will reduce the revenue we derive from WAYLIVRA. In addition, while AKCEA-ANGPTL3-L_{Rx} and WAYLIVRA use different mechanisms of action, if AKCEA-ANGPTL3-L_{Rx} can effectively lower triglyceride levels in FCS patients, it may likewise reduce the revenue we derive from WAYLIVRA.

If we cannot manufacture our drugs or contract with a third party to manufacture our drugs at costs that allow us to charge competitive prices to buyers, we will not be able to operate profitably.

To successfully commercialize TEGSEDI and, if approved, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, we will need to optimize and manage large-scale commercial manufacturing capabilities either on our own or through a third-party manufacturer. In addition, as our drug development pipeline matures, we will have a greater need for clinical study and commercial manufacturing capacity. We have no direct experience manufacturing pharmaceutical products of the chemical class represented by our drugs, called oligonucleotides, on a commercial scale for the systemic administration of a drug. We currently rely and expect to rely for the foreseeable future on Ionis' manufacturing capacity and efficiency and the capacity and efficiency of third parties to produce our oligonucleotide drugs, and our business could be negatively affected if Ionis and these third parties ceased to provide us with this capability for any reason. In addition, there are a small number of suppliers for certain raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, if we cannot continue to acquire raw materials from these suppliers on commercially reasonable terms or at all, we may be required to find alternative suppliers, which could be expensive and time consuming and negatively affect our ability to develop or commercialize our drugs in a timely manner or at all. We may not be able to manufacture our drugs at a cost or in quantities necessary to make commercially successful products.

We do not have long-term supply agreements for our drugs. We cannot guarantee that we will have a steady supply of drug to complete clinical studies, make registration batches for approval or satisfy market demand if commercialized at prices that are commercially acceptable. In addition, if we need to change manufacturers for any reason, we will need to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with verifying a new manufacturer could negatively affect our ability to develop drugs in a timely manner or within budget.

Also, manufacturers must adhere to the FDA's current Good Manufacturing Practices regulations and similar regulations in foreign countries, which the applicable regulatory authorities enforce through facilities inspection programs. Our contract manufacturers may not comply or maintain compliance with Good Manufacturing Practices, or similar foreign regulations. Non-compliance could significantly delay or prevent receipt of marketing authorization for our drugs, including authorizations for WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, or result in enforcement action after authorization that could limit the commercial success of our drugs, including WAYLIVRA, TEGSEDI, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development.

We depend on Ionis and third parties to conduct our clinical studies for our drugs and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on Ionis and independent clinical investigators, contract research organizations and other third-party service providers to conduct the clinical studies for our drugs and expect to continue to do so in the future. For example, we use clinical research organizations for the clinical studies for WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan, approved protocols for the study and applicable regulations. Ionis and third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these parties to carry out their obligations or a termination of our relationship with these third parties could delay or prevent the development, marketing authorization and commercialization of our drugs, including authorizations for WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development.

We may seek to form additional partnerships in the future with respect to WAYLIVRA, and our other drugs in development, and we may not realize the benefits of such partnerships.

Although we intend to develop and commercialize WAYLIVRA for patients with FCS and FPL ourselves, we may form partnerships, create joint ventures or collaborations or enter into licensing arrangements with third parties for the development and commercialization of our drugs in development. For example, we have granted PTC an exclusive license to commercialize WAYLIVRA in Latin America and certain Caribbean countries. We face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Any delays in entering into new strategic partnership agreements related to our drugs could delay the development and commercialization of our drugs and reduce their competitiveness even if they reach the market. Moreover, we may not be successful in our efforts to establish other strategic partnerships or other collaborative arrangements for any additional drugs because the potential partner may consider that our development pipeline is not advanced enough to justify a collaborative effort, or that WAYLIVRA and our other drugs in development do not have the requisite potential to demonstrate safety and efficacy in the target populations in other geographic markets. In addition, we will need to mutually agree with Ionis on the terms of any additional sublicenses to a third party for WAYLIVRA and our other drugs in development. If we cannot mutually agree on terms for a sublicense to a third party or if Ionis does not agree to a sublicense at all, it could delay our ability to develop and commercialize WAYLIVRA and our other drugs in development. Even if we are successful in establishing such a strategic partnership or collaboration, we cannot be certain that, following such a strategic transaction or collaboration, we will be able to progress the development and commercialization of the applicable drugs as envisioned, or that we will achieve the revenue that would justify such transaction. If we do not accurately evaluate the commercial potential or target market for a particular drug, we may relinquish valuable rights to that drug through future collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

Risks Related to Our Relationship with Ionis

Ionis controls the direction of our business, and the concentrated ownership of our common stock will prevent you and other stockholders from influencing significant decisions.

Ionis owns 67,383,965 shares of our common stock, or approximately 75 percent, of the economic interest and voting power of our outstanding common stock as of February 20, 2019, which ownership will be expected to increase further if we achieve certain milestone events and pay the associated milestone payment in shares of common stock pursuant to the payment election. As long as Ionis beneficially controls a majority of the voting power of our outstanding common stock, it will generally be able to determine the outcome of all corporate actions requiring stockholder approval, including the election and removal of directors. Even if Ionis were to control less than a majority of the voting power of our outstanding common stock, it may influence the outcome of such corporate actions so long as it owns a significant portion of our common stock. If Ionis continues to hold its shares of our common stock, it could remain our controlling stockholder for an extended period of time or indefinitely.

The licensing transaction with Ionis and the common stock issuances in connection with the achievement of the TEGSEDI regulatory milestones has increased Ionis' ownership percentage, and this increase, along with Ionis' increased reliance on Akcea as a commercialization partner, given that Akcea could now be commercializing at least two Ionis-developed products (WAYLIVRA and TEGSEDI), may increase the length of time during which Ionis will control us. As a general matter, the TEGSEDI license agreement and the related Investor Rights Agreement increased Ionis' control over our affairs. In addition, our TEGSEDI licensing agreement requires Ionis' consent to the budget related to the commercialization of TEGSEDI and AKCEA-TTR-L_{Rx}.

Ionis' interests may not be the same as, or may conflict with, the interests of our other stockholders. You will not be able to affect the outcome of any stockholder vote while Ionis controls the majority of the voting power of our outstanding common stock. As a result, Ionis can control, directly or indirectly and subject to applicable law, all matters affecting us, including:

- any determination with respect to our business strategy and policies, including the appointment and removal of officers and directors;
- any determinations with respect to mergers, business combinations or disposition of assets;
- our financing and dividend policy;
- compensation and benefit programs and other human resources policy decisions;
- termination of, changes to or determinations under our existing license agreements and services agreement with Ionis;
- changes to any other agreements that may adversely affect us; and
- determinations with respect to our tax returns.

Because Ionis' interests may differ from ours or yours, actions that Ionis takes with respect to us, as our controlling stockholder, may not be favorable to us or you.

As a "controlled company" under the marketplace rules of the Nasdaq Stock Market, we may rely on exemptions from certain corporate governance requirements that provide protection to stockholders of companies that are subject to such requirements.

Ionis beneficially owns more than 50% of the voting power of our outstanding common stock. As a result, we are a "controlled company" under the marketplace rules of the Nasdaq Stock Market, or Nasdaq, and eligible to rely on exemptions from Nasdaq corporate governance requirements generally obligating listed companies to maintain:

- A board of directors having a majority of independent directors;
- A compensation committee composed entirely of independent directors that approves the compensation payable to the company's chief executive officer and other executive officers; and
- A nominating committee composed entirely of independent directors that nominates candidates for election to the board of directors, or that recommends such candidates for nomination by the board of directors (or obligating the listed company to cause a majority of the board's independent directors to exercise this oversight of director nominations).

Currently, a majority of our board is made up of independent directors. As a controlled company, we have and in the future may avail ourselves of some of these exemptions. Accordingly, our stockholders may not have the same protections afforded to stockholders of companies that are subject to the Nasdaq corporate governance requirements described above.

If Ionis sells a controlling interest in our company to a third party in a private transaction, you may not realize a change of control premium on shares of our common stock, and we may become subject to the control of a presently unknown third party.

Ionis owns a significant equity interest in our company. This means that Ionis could choose to sell some or all of its shares of our common stock in a privately negotiated transaction, which, if sufficient in size, could result in a change of control of our company.

Ionis' ability to privately sell its shares of our common stock, with no requirement for a concurrent offer to be made to acquire your shares of our common stock, could prevent you from realizing any change of control premium on your shares of our common stock that may otherwise accrue to Ionis on its private sale of our common stock. Additionally, if Ionis privately sells its significant equity interest in our company, we may become subject to the control of a presently unknown third party. Such third party may have conflicts of interest with those of other stockholders. In addition, if Ionis sells a controlling interest in our company to a third party, such a sale could negatively impact or accelerate any future indebtedness we may incur, and negatively impact any other commercial agreements and relationships, all of which may adversely affect our ability to run our business as described herein and may have a material adverse effect on our operating results and financial condition.

Certain of our directors and officers may have actual or potential conflicts of interest because of their positions with Ionis.

Damien McDevitt, Chief Business Officer for Ionis, and B. Lynne Parshall, Senior Strategic Advisor and board member for Ionis, serve on our board of directors and retain their positions or engagements with Ionis. In addition, these individuals own Ionis equity and Ionis equity awards. Ionis common stock, options to purchase Ionis common stock and other Ionis equity awards represent a significant portion of these individuals' net worth. Their position at Ionis and the ownership of any Ionis equity or equity awards creates, or may create the appearance of, conflicts of interest when we ask these individuals to make decisions that could have different implications for Ionis than the decisions have for us. In addition, our certificate of incorporation provides for the allocation of certain corporate opportunities between us and Ionis. Under these provisions, neither Ionis or its other affiliates, nor any of their officers, directors, agents or stockholders, will have any obligation to present to us certain corporate opportunities. For example, a director of our company who also serves as a director, officer or employee of Ionis or any of its other affiliates may present to Ionis certain acquisitions, in-licenses, potential development programs or other opportunities that may be complementary to our business and, as a result, such opportunities may not be available to us. To the extent attractive corporate opportunities are allocated to Ionis or its other affiliates instead of to us, we may not be able to benefit from these opportunities.

The resources Ionis provides us under the license agreements and the services agreement may not be sufficient for us to operate as a standalone company, and we may experience difficulty in separating our resources from Ionis.

Because we have not operated separately from Ionis in the past, we may have difficulty doing so. We will need to acquire resources in addition to, and eventually in lieu of, those provided by Ionis to our company, and may also face difficulty in separating our resources from Ionis' resources and integrating newly acquired resources into our business. In addition, Ionis may prioritize its own research, development, manufacturing and other needs ahead of the services Ionis has agreed to provide us, or Ionis employees who conduct services for us may prioritize Ionis' interests over our interests. Our business, financial condition and results of operations could be harmed if we have difficulty operating as a standalone company, fail to acquire resources that prove to be important to our operations or incur unexpected costs in separating our resources from Ionis' resources or integrating newly acquired resources.

We may not realize the benefits of the licensing transaction with Ionis if we are unable to successfully transition, integrate and support the development and commercialization of TEGSEDI and AKCEA-TTR-L_{Rx}.

As a result of the licensing transaction with Ionis, we need to successfully transition, integrate and support the assets we acquired related to the commercialization and development of TEGSEDI and AKCEA-TTR-L_{Rx} if we are to realize any of the potential benefits of the licensing transaction. The failure to meet these integration challenges, including the addition of TEGSEDI commercial team and other employees from Ionis and the coordination across geographies between our headquarters in Massachusetts and our commercialization team in other locations, including major global markets, could seriously harm our results of operations. Our failure to implement an orderly integration could result in failure of, or delays in, the development or commercialization of TEGSEDI and AKCEA-TTR-L_{Rx}. Such failure or delay could adversely impact our business, results of operations, financial condition and prospects for future growth.

We will incur incremental costs as a standalone company.

Ionis currently performs or supports many important corporate functions for our company. Our consolidated financial statements reflect charges for these services on an allocation basis. Under our services agreement with Ionis we can use these Ionis services for a fixed term established on a service-by-service basis. However, we generally will have the right to terminate a service earlier if we give notice to Ionis. Partial reduction in the provision of any service requires Ionis' consent. In addition, either party will be able to terminate the agreement due to a material breach of the other party, upon prior written notice, subject to limited cure periods.

We will pay Ionis mutually agreed upon fees for these services, based on Ionis' costs of providing the services. Since we negotiated the services agreement in the context of a parent subsidiary relationship, the terms of the agreement, including the fees charged for the services, may be higher or lower than those that would be agreed to by parties bargaining at arm's length for similar services and may be higher or lower than the costs reflected in the allocations in our historical consolidated financial statements. Ionis will pass third party costs through to us at Ionis' cost. In addition, while Ionis provides us these services, our operational flexibility to modify or implement changes with respect to such services or the amounts we pay for them will be limited.

We may not be able to replace these services or enter into appropriate third-party agreements on terms and conditions, including cost, comparable to those that we will receive from Ionis under our services agreement. Additionally, after the agreement terminates, we may not sustain the services at the same levels or obtain the same benefits as when we were receiving such services and benefits from Ionis. When we begin to operate these functions separately, if we do not have our own adequate systems and business functions in place, or cannot obtain them from other providers, we may not operate our business effectively or at comparable costs, and our business may suffer. In addition, we have historically received informal support from Ionis, which may not be addressed in our services agreement. The level of this informal support will diminish and could end in the future.

We may not be able to fully realize the expected benefits of our license agreements with Ionis.

We have development, commercialization and license agreements with Ionis pursuant to which, subject to certain restrictions, we and Ionis will share development responsibilities for WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development. We are paying for research and development costs and reimbursing Ionis for Ionis' employees supporting our development activities. Until we build or acquire our own capabilities to replace those Ionis is providing to us, particularly development, regulatory and manufacturing services, we will be heavily dependent on Ionis.

While we and Ionis intend the license agreements, on the whole, to bolster our capabilities, certain terms of the license agreements and the other related agreements with Ionis may limit our ability to achieve the expected benefits of these transactions, including:

- a Joint Steering Committee, or JSC, having equal membership from us and Ionis, sets the development strategy for our drugs by mutual agreement. A Regulatory Sub-committee, established by the JSC and having equal membership from our company and Ionis, will set the regulatory strategy for each of our drugs by mutual agreement. If the JSC or the Regulatory Sub-committee cannot come to a mutual agreement, then this could delay our ability to develop and commercialize TEGSEDI, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development. In the event of a disagreement at the JSC related to TEGSEDI or AKCEA-TTR-L_{Rx}, Ionis has final decision-making authority on decisions relating to development matters, Akcea has final decision making authority on decision relating to commercial matters, and the holder of the regulatory approvals for a product in a country has final decision making authority for regulatory affairs;
- we will need to mutually agree with Ionis on the terms of any additional sublicense to a third party for WAYLIVRA and AKCEA-ANGPTL-L_{Rx}, and will need to obtain Ionis’ consent prior to granting any sublicense to a third party for TEGSEDI or AKCEA-TTR-L_{Rx}. If we cannot mutually agree on terms for a sublicense to a third party or if Ionis does not consent to a sublicense at all, it could delay or prevent our ability to develop and commercialize our drugs;
- we will need to obtain Ionis’ approval to in-license a product, acquire a product or acquire another company, until the time Ionis ceases to hold at least 50% of our outstanding capital stock; and
- there is nothing in our agreements with Ionis to prevent Ionis from developing and commercializing drugs targeting RNAs that are not apoC-III, Apo(a) or ANGPTL3 to pursue the same indications we are pursuing with our drugs.

Each of the foregoing terms and Ionis' other rights under the license agreements, could limit our ability to realize the expected benefits of the license agreements or otherwise limit our ability to pursue transactions or development efforts other stockholders may view as beneficial. Further, if Ionis does not continue to own a significant portion of our equity, Ionis' incentive to help us would be diminished. If we fail to achieve the expected benefits of our agreements with Ionis, it may be more difficult, time consuming or expensive for us to develop and commercialize WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development and continue the commercialization of TEGSEDI, or may result in our drugs being later to market than those of our competitors or prevent them from ever getting to market. If these events cause delays in new product development we could lose the first in class products in a given therapeutic area.

Risks Related to Our Intellectual Property

If we breach our obligations under any of our license agreements with Ionis, we could lose our rights to WAYLIVRA, TEGSEDI, AKCEA-TTR-L_{Rx} and our other drugs in development.

We obtained our rights to WAYLIVRA, TEGSEDI, AKCEA-TTR-L_{Rx} and our other drugs in development under our license agreements with Ionis. If we breach our obligations under these license agreements and, as a result, Ionis subsequently exercises its right to terminate it, we generally would not be able to continue to develop or commercialize TEGSEDI, WAYLIVRA, AKCEA-TTR-L_{Rx} and our other drugs in development that incorporate Ionis' intellectual property, and Ionis would receive a royalty-free, nonexclusive license to our improvements to those programs, meaning we would lose the benefits of our investment in these programs. If we breach our obligations under the license agreement with respect to AKCEA-APO(a)-L_{Rx} or AKCEA-APOCIII-L_{Rx} and, as a result, Ionis exercises its right to terminate it, then our strategic collaboration with Novartis would convert into a direct strategic collaboration between Novartis and Ionis, and Ionis would receive all of the revenue and other benefits associated with that strategic collaboration. Similarly, if we breach our obligations under the license agreement with respect to TEGSEDI or AKCEA-TTR-L_{Rx} and, as a result, Ionis exercises its right to terminate it, then our strategic collaboration with PTC in Latin America and certain Caribbean countries would convert into a direct strategic collaboration between PTC and Ionis, and Ionis would receive all of the revenue and other benefits associated with that strategic collaboration.

If we cannot protect our patent rights or our other proprietary rights, others may compete more effectively against us.

Our success depends to a significant degree upon whether we can continue to secure and maintain intellectual property rights that protect TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development. However, patents may not issue from any of our pending patent applications in the United States or in other countries and we may not be able to obtain, maintain or enforce our owned or licensed patents and other intellectual property rights which could impact our ability to compete effectively. In addition, the scope of any of our owned or licensed patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, other parties may successfully challenge, invalidate or circumvent our issued patents or patents licensed to us so that our patent rights do not create an effective competitive barrier or revenue source.

Composition of matter patents on the active pharmaceutical ingredient for a product are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. Our WAYLIVRA patent portfolio currently includes:

- issued patent claims to the specific antisense sequence and chemical composition of WAYLIVRA in the United States, Australia, and Europe;
- issued patent claims in the United States and Australia drawn to the use of antisense compounds complementary to an active region of human apoC-III messenger ribonucleic acid, including the site targeted by WAYLIVRA;
- additional patent applications designed to protect the WAYLIVRA composition in Canada; and
- additional methods of use in jurisdictions worldwide for WAYLIVRA.

The natural term of the issued U.S. patent covering the WAYLIVRA composition of matter will expire in 2023, but we plan to seek to extend the U.S. patent expiration beyond 2023 based upon the development and regulatory review period in the United States. The natural term of the granted European and Australian patents covering WAYLIVRA will expire in 2024, but we plan to seek to extend each of these patents beyond 2024 based upon the development and regulatory review periods in Europe and Australia.

The natural term of the last expiring issued U.S. patent covering the composition of matter of TEGSEDI will expire in 2031. Patents issued in other countries will have the same natural term. We plan to seek to extend the term of one patent covering TEGSEDI in the U.S., if approved, and any other jurisdictions where such extension is available, based upon the development and regulatory review periods for TEGSEDI and in accordance with applicable laws.

We cannot be certain that the U.S. Patent and Trademark Office, or U.S. PTO, and courts in the United States or the patent offices and courts in foreign countries will consider the claims in our owned or licensed patents and applications covering WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx} and our other drugs in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, including through legal action.

If we or any licensor partner loses or cannot obtain patent protection for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} or our other drugs in development it could have a material adverse impact on our business.

Intellectual property litigation could cause us to spend substantial resources and prevent us from pursuing our programs.

From time to time we may have to defend our intellectual property rights. If we are involved in an intellectual property dispute, we may need to litigate to defend our rights or assert them against others. Disputes can involve arbitration, litigation or proceedings declared by the U.S. PTO or the International Trade Commission or foreign patent authorities. 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 adequately conduct such litigation or proceedings. 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 and more mature and developed intellectual property portfolios.

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 and the ability of our strategic partners to develop, manufacture, market and sell our drugs and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. Extensive litigation regarding patents and other intellectual property rights is common in the biotechnology and pharmaceutical industries. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our drugs and technology, including interference, derivation, reexamination, post-grant review, opposition, cancellation or similar proceedings before the U.S. PTO or its foreign counterparts.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. For example, a potential competitor was issued a patent which they have broadly characterized in their annual report on Form 10-K for the year ended December 31, 2017 as being directed to single-stranded antisense polynucleotide molecules capable of inhibiting expression of the human transthyretin gene, and having certain combinations of structural features. This third party has also attempted to broadly characterize certain other patents that they hold. While we believe that we would have substantial defenses in the event this competitor brought a claim against us with respect to TEGSEDI or AKCEA-TTR-L_{Rx}, patent litigation is inherently uncertain, involves substantial cost and is a distraction to management. Moreover, our stock price may be impacted by the existence of or developments during a litigation, even developments that are preliminary in nature.

We may not be aware of all such intellectual property rights potentially relating to our drugs and their uses. If a third party claims that WAYLIVRA, TEGSEDI, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, our other drugs in development or our technology infringe its patents or other intellectual property rights, we or our partners may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or patent applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially for the first 18 months. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain. Thus, we do not know with certainty that our drugs or our intended commercialization thereof, does and will not infringe or otherwise violate any third party's intellectual property.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on our drugs in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those we could obtain in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products. In addition, competitors may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patent rights or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology. This could make it difficult for us to stop competitors from infringing our patent rights or misappropriating our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit our right to enforce our patent rights against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. We must ultimately seek patent protection on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

In addition, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent rights at risk of being invalidated or interpreted narrowly, could put our owned or licensed patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent protection for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, and our other drugs in development, our business may be materially harmed.

Depending upon the timing, duration and specifics of the first FDA marketing authorization of TEGSEDI, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}, and our other drugs in development, a United States patent that we own or license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments allow the owner of an approved product to extend patent protection for up to five years as compensation for patent term lost during product development and the FDA regulatory review process. During this period of extension, the scope of protection is limited to the approved product and approved uses.

In 2018 we applied for patent term extensions to U.S. patents covering the TEGSEDI compound, composition and uses to recapture a portion of the term lost during regulatory review. Although we have applied for patent term extension for TEGSEDI, and plan on seeking patent term restoration for our other products, we may not succeed if, for example, we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we cannot obtain patent term restoration or the term of any such patent restoration is less than we request, our competitors may enter the market and compete against us sooner than we anticipate, and our ability to generate revenue could be materially adversely affected.

Changes in United States patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

Recent United States Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the United States Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

If we and our partners do not adequately protect the trademarks and trade names for our products, then we and our partners may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our competitors or other third parties may challenge, infringe or circumvent the trademarks or trade names for our products. We and our partners may not be able to protect these trademarks and trade names. In addition, if the trademarks or trade names for one of our products infringe the rights of others, we or our partners may be forced to stop using the trademarks or trade names, which we need for name recognition in our markets of interest. If we cannot establish name recognition based on our trademarks and trade names, we and our partners may not be able to compete effectively and our business may be adversely affected.

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 make compounds that are similar to our drugs but that are not covered by the claims of the patents that we own or have exclusively licensed;
- we, or our license partners or current or future strategic partners, 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 license partners or current or future strategic partners, might not have been the first to file patent applications covering our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- our pending licensed patent applications or those that we own in the future may not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including 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; and
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business, results of operations and prospects.

Risks Related to Our Business and Industry

We will need to significantly increase the size of our organization, and we may experience difficulties in managing growth.

We are currently a small company. To continue the commercialization of TEGSEDI and commercialize our drugs in development that we are responsible for commercializing, we will need to increase our operations and expand our use of third-party contractors. We plan to continue to build our compliance, financial and operating infrastructure to ensure the maintenance of a well-managed company including hiring additional staff within our regulatory, clinical and medical affairs groups and an in-house commercial organization initially focused on marketing and selling TEGSEDI and, if approved, WAYLIVRA. We have added a significant number of new employees to our sales and marketing capability to commercialize TEGSEDI.

We may also anticipate needs for growth that do not materialize. For example, in anticipation of WAYLIVRA's potential approval, we added a significant number of new employees to our sales and marketing capability to develop WAYLIVRA in the second half of 2017. However, as a result of our receipt of a complete response letter, or CRL, from the FDA regarding the new drug application for WAYLIVRA, on September 6, 2018, we enacted a plan to reorganize our workforce to better align with the immediate needs of our business. In connection with this reorganization plan, we reduced our workforce by approximately 12%. If WAYLIVRA is subsequently approved in the United States, we will again need to increase our operations and expand our use of third-party contractors. We cannot assure you that we will not build out our compliance, financial or operating infrastructure again in anticipation of developments that do not occur or that occur later than we anticipate.

The current and future growth will impose significant added responsibilities on our management, including the need to maintain, integrate, optimize and manage additional employees. In addition, to meet our obligations as a public company, we will need to increase our general and administrative capabilities. Our current management, personnel and systems may not be adequate to support this growth. Our future financial performance and our ability to commercialize our drugs and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to:

- manage the manufacturing of our drugs for clinical and commercial use;
- integrate current and additional management, administrative, financial and sales and marketing personnel;
- optimize and manage a marketing and sales infrastructure;
- maintain personnel necessary to effectively commercialize TEGSEDI and, if approved, WAYLIVRA and our other drugs in development;
- manage our clinical studies and the regulatory process effectively;
- develop our administrative, accounting and management information systems and controls; and
- hire and train additional qualified personnel.

Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to successfully manage future market opportunities or our relationships with customers and other third parties.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter into clinical trials, when we anticipate completing a clinical study, when we anticipate filing an application for marketing authorization, or when we or our partners plan to commercially launch a drug. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside of our control. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to WAYLIVRA, TEGSEDI, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development, the price of our securities could decrease.

The loss of key personnel, or if we cannot attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers that would prevent them from leaving us. The loss of management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform development work and marketing, sales and commercial support personnel to perform commercialization activities. We may not be able to attract and retain skilled and experienced scientific and commercial personnel on acceptable terms because of intense competition for experienced personnel among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to successfully complete clinical studies, obtain regulatory approvals or effectively commercialize drugs may make it more challenging to recruit and retain qualified personnel.

We are exposed to potential product liability claims, and insurance against these claims may not be available to us at a reasonable rate in the future or at all.

Our business exposes us to potential product liability risks that are inherent in the testing, manufacturing, marketing and sale of therapeutic products, including potential product liability claims related to TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development. We have clinical study insurance coverage and commercial product liability insurance coverage. In addition, Novartis has agreed to indemnify us against specific claims arising from Novartis' development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, and PTC has agreed to indemnify us against specific claims arising from PTC’s commercialization of TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. However, this insurance coverage and indemnities may not be adequate to cover claims against us. Insurance may not be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, products liability claims may result in decreased demand for our drug products, injury to our reputation, withdrawal of clinical study volunteers and loss of revenue. Thus, whether or not we are insured or indemnified, a product liability claim or product recall may result in losses that could be material.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be hazardous to human health and safety or the environment. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our development, manufacturing and distribution efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance in amounts and types that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our development, manufacturing or commercialization efforts caused by contamination, and the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

A variety of risks associated with operating our business and marketing our drugs internationally could materially adversely affect our business.

In addition to our U.S. operations, we are commercializing TEGSEDI in Europe and Canada and, following approval, plan to establish operations to commercialize our products in other countries globally. We face risks associated with our current and planned international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations we are subject to numerous risks associated with international business activities, including:

- compliance with differing or unexpected regulatory requirements for our drugs and foreign employees;
- complexities associated with managing multiple payor reimbursement regimes, government payors or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;
- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism or political instability in particular foreign countries;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States; and
- changes in diplomatic and trade relationships.

The United Kingdom’s anticipated exit from the EU could increase these risks.

Our business activities outside of the United States are subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the United Kingdom's Bribery Act 2010. In many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. In particular, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions. Violation of these laws may result in civil or criminal sanctions, which could include monetary fines, criminal penalties, and disgorgement of past profits, which could have a material adverse impact on our business and financial condition.

The impact on us of the vote by the United Kingdom to leave the European Union cannot be predicted.

On June 23, 2016, the United Kingdom, or the UK, voted to leave the EU in an advisory referendum, which is generally referred to as Brexit. On March 29, 2017, the UK delivered notice under Article 50 of the Lisbon Treaty of its intent to leave the EU, beginning a two year negotiation period for the UK and the 27 remaining members of the EU to reach agreement on the terms of Brexit. The UK is a significant pharmaceutical market, and Brexit may lead to legal uncertainty and potentially divergent laws and regulations between the UK and the EU as the UK determines which EU laws to replicate or replace. We cannot predict whether or not the UK will significantly alter its current laws and regulations in respect of the pharmaceutical industry and, if so, what impact any such alteration would have on us or our business.

As part of Brexit, the EMA, currently situated in London, is expected to relocate to Amsterdam. There is a risk that the relocation process will interrupt current administrative routines and occupy resources, which may lead to delays in the EMA’s handling of our WAYLIVRA application and generally adversely affect our dealings with the EMA. Further, there is considerable uncertainty resulting from a lack of precedent and the complexity of the UK and EU’s intertwined legal regimes as to how Brexit will impact the life sciences industry in Europe, including our company, including with respect to ongoing or future clinical trials. The impact will largely depend on the model and means by which the UK’s relationship with the EU is governed post-Brexit. For example, following Brexit, the UK will no longer be covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products, including our product candidates, will be required in the UK, the potential process for which is currently unclear. Brexit may adversely affect and delay our ability to commercialize, market and sell our product candidates in the UK. Brexit may also result in a reduction of funding to the EMA if the UK no longer makes financial contributions to European institutions, such as the EMA. If UK funding is so reduced, it could create delays in the EMA issuing regulatory approvals for our product candidates and, accordingly, have a material adverse effect on our business, financial condition, results or prospects.

If a natural or man-made disaster strikes our development or manufacturing facilities or otherwise affects our business, it could delay our progress developing and commercializing our drugs.

We currently rely on Ionis to manufacture our clinical supplies in a manufacturing facility located in Carlsbad, California and third party contract manufacturing organizations to manufacture active pharmaceutical ingredient and finished drug product for TEGSEDI. The facilities and the equipment required to develop and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Natural or man-made disasters, including, without limitation, earthquakes, floods, fires and acts of terrorism may harm these facilities. If a disaster affects these facilities, our and our partners' development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, a shutdown of the U.S. government, including the FDA could harm or delay our development and commercialization activities.

Our business and operations would suffer in the event of computer system failures.

We are dependent upon our own or third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity. Cyber-attacks could include the deployment of

harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and/or result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. In addition, our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyber-attacks and other related breaches.

Risks Related to Our Common Stock

We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies" including, but not limited to, the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We cannot predict if investors will find our common stock less attractive if we choose to rely on 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.

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

Prior to the completion of our IPO in July 2017, no public market for our common stock existed. An active public trading market for our common stock may not be sustained. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair value of your shares. An inactive market may also impair our ability to raise capital to continue to fund operations by selling shares. Additionally, as of February 20, 2019, Ionis owns approximately 75 percent of our outstanding common stock. Ionis intends to hold its shares of our common stock for the foreseeable future, which could reduce the public market for our stock.

The market price for our common stock may be volatile, which could contribute to the loss of your investment.

Fluctuations in the price of our common stock could contribute to the loss of all or part of your investment. There has been a public market for our common stock for a limited period of time. The trading price of our common stock is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. Any of the factors listed below could have a material adverse effect on your investment in our common stock and our common stock may trade at prices significantly below your purchase price. In such circumstances the trading price of our common stock may not recover and may experience a further decline.

Factors affecting the trading price of our common stock may include:

- our failure to effectively develop and commercialize TEGSEDI, WAYLIVRA and our other drugs in development;
- Novartis' failure to exercise its option and/or effectively develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} to the extent it exercises its option to license those drugs from us;
- PTC’s failure to effectively commercialize TEGSEDI or WAYLIVRA in Latin America and certain Caribbean countries;
- changes in the market's expectations about our operating results;
- adverse results or delays in preclinical or clinical studies;

- our decision to initiate a clinical study, not to initiate a clinical study or to terminate an existing clinical study;
- adverse regulatory decisions, including failure to receive additional regulatory approvals for TEGSEDI, or regulatory approval for WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development;
- success or failure of competitive products or antisense drugs more generally;
- adverse developments concerning our manufacturers or our strategic partnerships;
- inability to obtain adequate product supply for any drug for clinical studies or commercial sale or inability to do so at acceptable prices;
- the termination of a strategic partnership or the inability to establish additional strategic partnerships;
- unanticipated serious safety concerns related to the use of TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development;
- adverse safety or other clinical results, such as those that have occurred in the past or that may occur in the future, related to drugs being developed by Ionis or other companies that are or may be perceived to be similar to our drugs;
- our ability to effectively manage our growth;
- the size and growth, if any, of the targeted market;
- our operating results do not meet the expectation of securities analysts or investors in a particular period;
- actual or anticipated fluctuations in our quarterly financial results or the quarterly financial results of companies perceived to be similar to us;
- securities analysts do not publish reports about us or our business or publish negative reports;
- changes in financial estimates and recommendations by securities analysts concerning our company, our market opportunity, or the biotechnology and pharmaceutical industries in general;
- operating and stock price performance of other companies that investors deem comparable to us;
- overall performance of the equity markets;
- announcements by us or our competitors of acquisitions, new drugs or programs, significant contracts, commercial relationships or capital commitments;
- our and our strategic partners' ability to successfully market TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development;
- changes in laws and regulations affecting our business, including but not limited to clinical study requirements for approvals;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain and maintain patent protection for TEGSEDI, WAYLIVRA, AKCEA-APO(a)-$L_{Rx,}$ AKCEA-TTR-L_{Rx} and our other drugs in development;
- commencement of, or involvement in, litigation involving our company, our general industry, or both;
- changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
- the volume of shares of our common stock available for public sale;
- additions or departures of key scientific or management personnel;
- any major change in our board or management;
- changes in accounting practices;
- ineffectiveness of our internal control over financial reporting;
- significant changes in our relationship with Ionis;
- sales of substantial amounts of common stock by our directors, executive officers or significant stockholders or the perception that such sales could occur; and
- general economic and political conditions such as recessions, interest rates, fuel prices, elections, drug pricing policies, international currency fluctuations and acts of war or terrorism.

Broad market and industry factors may materially harm the market price of our common stock irrespective of our operating performance. The stock market in general, and NASDAQ and the market for biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies which investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

Sales of a substantial number of shares of our common stock by our existing stockholders in the public market may cause our stock price to decline.

Sales of our common stock in the public market, or the perception that these sales may occur, could cause the market price of our common stock to decline. Novartis has agreed that it will not sell any of its shares until the earlier of January 5, 2020 or six months after we stop developing a drug under our agreement with Novartis. Thereafter, Novartis may only sell a limited number of shares each day. In addition, as of February 20, 2019 Ionis owns 67,383,965 shares, or approximately 75 percent, of our common stock. While the shares of common stock held by Ionis are eligible for sale in the public market, any sales by Ionis will be subject to volume limitations under Rule 144 under the Securities Act of 1933, as amended, or the Securities Act. In addition, 18,500,000 shares of common stock that are either subject to outstanding options or reserved for future issuance under our employee benefit plans are eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules, the lock-up agreements and Rule 144 and Rule 701 under the Securities Act. To the extent the holders of these shares sell them into the market or our stockholders believe these sales might occur, the market price of our common stock could decline.

We cannot predict with certainty whether or when Ionis will sell a substantial number of shares of our common stock. Ionis' sale of a substantial number of shares, or a perception that such sales could occur, could significantly reduce the market price of our common stock.

We do not expect to pay any cash dividends for the foreseeable future.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any cash dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our operations. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

Changes in tax laws, regulations and treaties could affect our future taxable income.

A change in tax laws, treaties or regulations, or their interpretation, of any country in which we operate could materially affect us. For Example, on December 22, 2017, the United States enacted H.R.1., known as the Tax Cuts and Jobs Act, which represented a substantial change to tax laws in the United States, but which did not have a material impact on our financial statements because we maintain a valuation allowance on all our net operating losses and other deferred tax assets. However, any future changes in tax laws in any U.S. or non-U.S jurisdictions could have a material effect on our business.

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and sales taxes in the United States and foreign income taxes, withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our worldwide provision for taxes. During the ordinary course of business, there are many activities and transactions for which the ultimate tax determination is uncertain. In addition, our tax obligations and effective tax rates could be adversely affected by changes in the relevant tax, accounting and other laws, regulations, principles and interpretations, including those relating to income tax nexus, by recognizing tax losses or lower than anticipated earnings in jurisdictions where we have lower statutory rates and higher than anticipated earnings in jurisdictions where we have higher statutory rates, by changes in foreign currency exchange rates, or by changes in the valuation of our deferred tax assets and liabilities. We may be audited in various jurisdictions, and such jurisdictions may assess additional taxes, sales taxes and value-added taxes against us. Although we believe our tax estimates are reasonable, the final determination of any tax audits or litigation could be materially different from our historical tax provisions and accruals, which could have a material adverse effect on our operating results or cash flows in the period for which a determination is made.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Provisions in our amended and restated certificate of incorporation, our amended and restated bylaws and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and bylaws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- specify that only board of directors or holders of greater than 10% of our common stock can call special meetings of our stockholders;
- prohibit stockholder action by written consent once Ionis no longer holds a majority of our voting power;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that a majority of directors then in office, even though less than a quorum, may fill vacancies on our board of directors;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated bylaws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management. Further, Novartis has agreed that until Novartis holds less than 7.5% of our outstanding common stock, Novartis will vote the Novartis Private Placement Shares consistent with the recommendation of our board of directors. Although Novartis has retained the right to vote the Novartis Private Placement Shares in its sole discretion in connection with certain enumerated matters, including any transaction which would result in our change of control, our agreement with Novartis may nevertheless delay or prevent changes in our management or board of directors.

In addition, because we are incorporated in the State of Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit your opportunity to receive a premium for your shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our bylaws designate the Court of Chancery of the State of Delaware and federal court within the State of Delaware as the exclusive forum for certain types of actions and proceedings that our stockholders may initiate, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our bylaws provide that, subject to limited exceptions, the Court of Chancery of the State of Delaware and federal court within the State of Delaware will be exclusive forums for any:

- derivative action or proceeding brought on our behalf;
- action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders;
- action asserting a claim against us arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or
- other action asserting a claim against us that is governed by the internal affairs doctrine.

Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our bylaws described above. This choice of forum 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 employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our corporate headquarters is located in Boston, Massachusetts. We currently occupy approximately 30,175 square feet of office space. Our lease expires in November 2028. We also lease approximately 4,723 square feet of office space located in Carlsbad, California, which lease is set to expire in June 2023.

Item 3. Legal Proceedings

From time to time, we may be involved in various claims and legal proceedings relating to claims arising out of our operations. We are not currently a party to any legal proceedings that, in the opinion of our management, are likely to have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

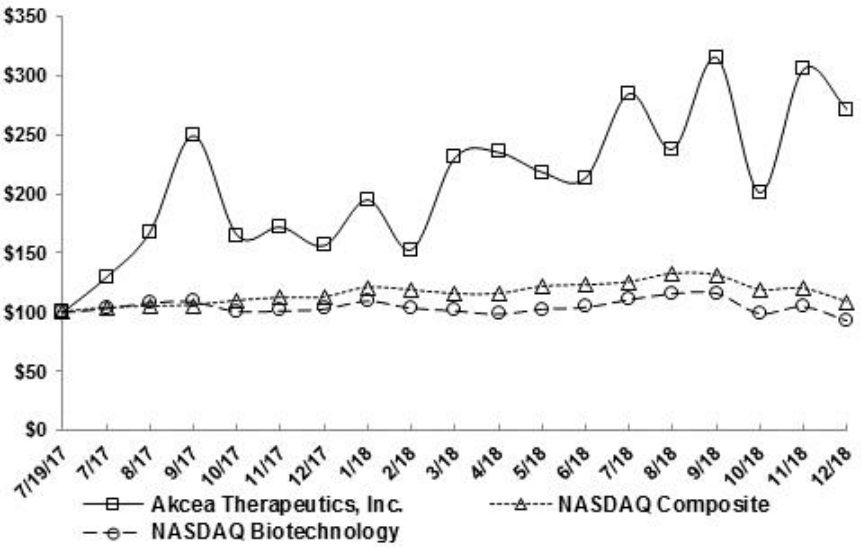
Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "AKCA." Prior to our initial public offering, or IPO, on July 19, 2017, there was no public trading market for our common stock. Our initial public offering was priced at $8.00 per share on July 17, 2017. On February 20, 2019, the closing price of our common stock on The Nasdaq Global Select Market was $26.25 per share.

As of February 20, 2019, there were 8 stockholders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of stockholders represented by these record holders.

Set forth below is a chart comparing the total return on an indexed basis of $100 invested on July 19, 2017, which is the date our shares began trading, in our common stock, the NASDAQ Composite Index (total return) and the NASDAQ Biotechnology Index through December 31, 2018. The total return assumes reinvestment of dividends. Historical stockholder return is not necessarily indicative of the performance to be expected for any future periods.

Performance Graph (1)

Comparison of 18 Month Cumulative Total Return*
Among Akcea Therapeutics, Inc., the NASDAQ Composite Index and the NASDAQ Biotechnology Index



*$100 invested on July 19, 2017 in stock or June 30, 2017 index, including reinvestment of dividends. Fiscal year ending December 31.

(1) This section is not "soliciting material," is not deemed "filed" with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

Recent Sale of Unregistered Securities

During the year ended December 31, 2018, we did not issue or sell any unregistered securities not previously disclosed in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K.

Use of Proceeds from Public Offering of Our Common Stock

On July 19, 2017, we closed our IPO of 17,968,750 shares of common stock at an offering price of $8.00 per share, resulting in gross proceeds to us of approximately $143.8 million. All of the shares issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-216949), which was declared effective by the SEC on July 13, 2017. Cowen and Company, LLC, Stifel, Nicolaus & Company, Incorporated and Wells Fargo Securities, LLC acted as joint book-running managers for our initial public offering and BMO Capital Markets Corp. acted as lead manager for our initial public offering. The offering commenced on June 20, 2017 and did not terminate before all of the securities registered in the registration statement were sold.

As of December 31, 2018, we have applied all of the offering proceeds in accordance with the planned use of proceeds from our offering as described in final prospectus for our IPO dated July 13, 2017 and filed with the SEC pursuant to Rule 424(b)(4). As of December 31, 2018, all expenses incurred in connection with our initial public offering had been paid.

Purchase of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Selected Financial Data

This selected financial data should be read in conjunction with our audited consolidated financial statements and accompanying notes and Management's Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Annual Report on Form 10-K. Our consolidated financial information may not be indicative of our future performance. Set forth below are our selected consolidated financial data (in thousands, except per share amounts):

	Years Ended December 31,				
	2018	2017 (1) (as revised)	2016	2015	2014
Consolidated Statement of Operations Data:					
Product revenue	$ 2,237	$ —	$ —	$ —	$ —
Licensing revenue	$ 12,000	$ —	$ —	$ —	$ —
Research and development revenue under collaborative agreements	$ 50,630	$ 43,401	$ —	$ —	$ —
Cost of sales - product	$ 1,820	$ —	$ —	$ —	$ —
Cost of sales - intangible asset amortization	$ 2,713	$ —	$ —	$ —	$ —
Cost of license	$ 7,200	$ —	$ —	$ —	$ —
Research and development expenses	$ 130,340	$ 126,890	$ 68,459	$ 50,885	$ 29,028
Selling, general and administrative expenses	$ 153,610	$ 36,981	$ 15,053	$ 10,553	$ 995
Net loss	$ (225,821)	$ (121,559)	$ (83,217)	$ (61,422)	$ (30,023)
Net loss per share of preferred stock, basic and diluted	$ —	$ (1.80)	$ (2.88)	$ (2.13)	$ (1.04)
Weighted-average shares of preferred stock outstanding, basic and diluted	—	15,748	28,885	28,885	28,885
Net loss per share of common stock owned by Ionis, basic and diluted	$ (2.74)	$ (3.08)	$ —	$ —	$ —
Weighted-average shares of common stock outstanding owned by Ionis, basic and diluted	59,812,394	20,669,446	—	—	—
Net loss per share of common stock owned by others, basic and diluted	$ (2.87)	$ (3.08)	$ —	$ —	$ —
Weighted-average shares of common stock outstanding owned by others, basic and diluted	21,553,407	9,593,322	—	—	—

	As of December 31,			
	2018	2017 (1) (as revised)	2016	2015
Consolidated Balance Sheet:				
Cash, cash equivalents and short-term investments	$ 252,609	$ 260,130	$ 7,857	$ 64,310
Working capital	$ 186,574	$ 178,379	$ (19,344)	$ 53,761
Total assets	$ 365,261	$ 268,804	$ 10,684	$ 66,067
Payable to Ionis	$ 18,901	$ 14,365	$ 24,355	$ 9,198
Series A convertible preferred stock	$ —	$ —	$ 100,000	$ 100,000
Common stock and additional paid-in capital	$ 799,090	$ 464,497	$ —	$ —
Accumulated deficit	$ (522,042)	$ (296,221)	$ (174,662)	$ (91,445)
Stockholders' equity (deficit)	$ 276,724	$ 167,825	$ (17,747)	$ 55,267

(1) Reflects the impact of our adoption of the new revenue recognition accounting standard in 2018 (Topic 606). For additional details about our adoption of Topic 606, see Note 2, *Summary of Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements. This change is not reflected in our consolidated statement of operations data for 2015 or 2014 or in our consolidated balance sheet data for 2016 or 2015 as we did not have any revenues during these periods.

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

This financial review presents our operating results for each of the three years in the period ended December 31, 2018, and our financial condition at December 31, 2018. Except for the historical information contained herein, the following discussion contains forward-looking statements which are subject to known and unknown risks, uncertainties and other factors that may cause our actual results to differ materially from those expressed or implied by such forward-looking statements. We discuss such risks, uncertainties and other factors throughout this report and specifically under Item 1A of Part I of this report, "Risk Factors." In addition, the following review should be read in connection with the information presented in our consolidated financial statements and the related notes to our consolidated financial statements as indexed on page F-1.

Overview

We are a commercial stage biopharmaceutical company developing and marketing drugs globally to treat patients with rare and serious diseases. We are bringing novel and transformative medicines to patients by driving clinical program execution, understanding patient and physician needs, preparing the market, creating market access, and commercializing our products on a global basis. As an affiliate of Ionis Pharmaceuticals, Inc., or Ionis, we have a robust portfolio of development-, registration- and commercial-stage drugs covering multiple targets and diseases using antisense therapeutics. Our immediate focus is on the commercial launch of our first commercially approved therapy, TEGSEDI in the United States, or U.S., the European Union, or E.U., and Canada. TEGSEDI treats the polyneuropathy caused by hereditary transthyretin-mediated amyloidosis, or hATTR amyloidosis, in adults. We are also focused on commercial preparations for WAYLIVRA in the E.U. and on regulatory discussions for WAYLIVRA in the U.S. and Canada. The Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, we plan to leverage our existing commercial infrastructure in Europe to market WAYLIVRA. FCS is an ultra-rare, devastating hereditary disease that causes unpredictable and potentially fatal acute pancreatitis, chronic complications due to permanent organ damage, and a severe impact on daily living. The hallmark of FCS is extremely elevated triglycerides. There are approximately 3,000 to 5,000 patients with FCS worldwide. We are advancing a mature pipeline of novel drugs with the potential to treat multiple diseases. TEGSEDI, WAYLIVRA and our pipeline drugs, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-TTR-L_{Rx}, are all based on Ionis' antisense technology platform.

We are continuing to build our current commercial infrastructure to support TEGSEDI, and plan to use this infrastructure to support WAYLIVRA in the E.U. and the other drugs in our pipeline, if approved, as we anticipate further commercialization in serious and rare diseases. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed rare and serious diseases will allow us to partner efficiently and effectively with the specialized medical community that supports these underserved patient communities. Our supply chain is fully operational in both the U.S. and E.U. To further support the hATTR amyloidosis community, Akcea and Ambry Genetics Corporation, or Ambry, a Konica Minolta company, launched hATTR Compass™ in the U.S. and Canada, a no-cost, confidential genetic testing and genetic counseling program for people with suspected hATTR amyloidosis. This program is intended to empower people with accurate genetic information, so they can make informed decisions about their healthcare.

In 2018, we obtained TEGSEDI and AKCEA-TTR-L_{Rx}, the ligand conjugated antisense, or LICA, drug in development for TTR, under an exclusive license from Ionis. With the licensing agreement, we have expanded our efforts to treat people with serious and under-served rare diseases focusing on transthyretin amyloidosis, or ATTR amyloidosis, and cardiometabolic diseases.

ATTR

TEGSEDI is an antisense drug designed to reduce the production of the TTR protein. In patients with hATTR amyloidosis, a severe, rare and fatal genetic disease, both the hereditary and wild-type, or wt, TTR protein builds up as fibrils in tissues, such as the peripheral nerves, heart, gastrointestinal system, eyes, kidneys, central nervous system, thyroid and bone marrow. The presence of TTR fibrils interferes with the normal functions of these tissues. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to sensory, motor and autonomic dysfunction often having debilitating effects on multiple aspects of a patient's life and eventually leads to death.

We estimate that there are approximately 50,000 patients globally with hATTR amyloidosis, the majority of whom have symptoms of polyneuropathy.

TEGSEDI was discovered and developed by Ionis Pharmaceuticals and was licensed by us in April 2018. In addition to TEGSEDI, we and Ionis are developing AKCEA-TTR-L_{Rx} for hereditary and wild-type forms of transthyretin amyloidosis, or ATTR amyloidosis. We initiated clinical development of AKCEA-TTR-L_{Rx} in 2018.

Cardiometabolic

Our lipid/cardiometabolic drugs, WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-ANGPTL3-L_{Rx} and AKCEA-APOCIII-L_{Rx}, are all based on antisense technology developed by Ionis. We are focused on commercial preparations for WAYLIVRA in the E.U. and on regulatory discussions for WAYLIVRA the U.S. and Canada. The Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, has adopted a positive opinion recommending conditional marketing authorization of WAYLIVRA as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, who are at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. The positive opinion will now be referred to the EC, which grants marketing authorization for medicines in the European Union, as well as to European Economic Area members Iceland, Liechtenstein and Norway. With this positive opinion, and, pending adoption of the positive opinion by the EC, we plan to leverage our existing commercial infrastructure in Europe to market WAYLIVRA. On May 10, 2018, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted to support approval of WAYLIVRA for the treatment of people with FCS. On August 27, 2018, we and Ionis announced that we received a Complete Response Letter from the Division of Metabolism and Endocrinology Products of the FDA regarding the New Drug Application for WAYLIVRA. The FDA did not cite any new concerns beyond those described in the advisory committee briefing book, in which the main areas of focus were the dosing schedule and management of thrombocytopenia. We continue to feel strongly that WAYLIVRA demonstrates a favorable benefit/risk profile in people with FCS, as was reflected in the positive outcome from the Advisory Committee meeting. We received a preliminary notification of a Notice of Noncompliance withdrawal letter, or NON-W, from Health Canada for WAYLIVRA. We and Ionis are engaged with the FDA and plan to work with Health Canada to confirm a path forward for WAYLIVRA.

FCS is a severe and rare lipid disorder characterized by extremely elevated levels of triglycerides. FCS has life-threatening consequences such as acute pancreatitis and the lives of patients with this disease are impacted daily by the associated symptoms. In our clinical program, we have observed consistent and substantial (>70%) decreases in triglycerides and improvements in other manifestations of FCS, including pancreatitis attacks and abdominal pain. We believe the safety and efficacy data from the WAYLIVRA program demonstrate a favorable risk-benefit profile for patients with FCS. WAYLIVRA is also in Phase 3 clinical development for the treatment of familial partial lipodystrophy, or FPL. Our other three lipid/cardiometabolic drugs are currently in Phase 2 clinical development.

Commercial Infrastructure

We are continuing to build our global infrastructure as we begin to commercialize TEGSEDI and prepare to commercialize WAYLIVRA in the E.U., and we have commercial teams in place in the U.S., E.U. and Canada. In addition, in August 2018, we entered into a licensing agreement with PTC Therapeutics International Limited, or PTC Therapeutics, to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. A key element of our commercial strategy is to provide the specialized, patient-centric support required to successfully address rare disease patient populations. We believe our focus on treating patients with inadequately addressed rare and serious diseases will allow us to partner efficiently and effectively with the specialized medical community that supports these underserved patient communities.

To maximize the commercial potential of two of the drugs in our pipeline, we initiated a strategic collaboration with Novartis Pharma AG, or Novartis, for the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. In February 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx}. Novartis is currently preparing to initiate a Phase 3 study of AKCEA-APO(a)-L_{Rx} in patients with established cardiovascular disease (CVD) and elevated levels of lipoprotein(a), or Lp(a). We believe Novartis brings significant resources and expertise to the collaboration that can accelerate our ability to deliver these potential therapies to the large populations of patients who have high cardiovascular risk due to inadequately treated lipid disorders. As part of our collaboration, we received $75.0 million in an upfront option payment, of which we retained $60.0 million and paid $15.0 million to Ionis as a sublicense fee. We also earned a $150.0 million license fee when Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} of which we will pay $75.0 million to Ionis as a sublicense fee. We will pay Ionis the sublicense fee in Akcea common stock. Novartis is now responsible for all future development and commercialization activities for AKCEA-APO(a)-L_{Rx}. We are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APO(a)-L_{Rx} from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. In connection with Novartis' exercise of its option to

exclusively license AKCEA-APO(a)-L_{Rx}, Akcea and Novartis established a more definitive framework under which they would negotiate the co-commercialization of AKCEA-APO(a)-L_{Rx} between the two companies in selected markets. Included in this framework is an option by which Novartis could solely commercialize AKCEA-APO(a)-L_{Rx} in exchange for Novartis paying Akcea increased commercial milestone payments based on sales of AKCEA-APO(a)-L_{Rx}. We will share any license fees, milestone payments and royalties equally with Ionis.

For AKCEA-APOCIII-L_{Rx}, under our agreement with Novartis, after we complete Phase 2 development and if Novartis exercises its option to license AKCEA-APOCIII-L_{Rx}, we would receive an additional $150.0 million license fee which we would also share equally with Ionis. If exercised, Novartis would conduct and pay for a Phase 3 cardiovascular outcome study in patients with hypertriglyceridemia and prior cardiovascular risk. If approved, Novartis would commercialize AKCEA-APOCIII-L_{Rx} worldwide. Novartis will have 60 days plus additional time that could be required for Hart-Scott-Rodino, or HSR, filing and review following the end-of-Phase 2 meeting to exercise its option for AKCEA-APOCIII-L_{Rx}. As part of the collaboration, we may co-commercialize AKCEA-APOCIII-L_{Rx} in selected markets, on mutually agreed terms and conditions. Similar to AKCEA-APO(a)-L_{Rx}, we are eligible to receive license fees, milestone payments and royalties on sales of AKCEA-APOCIII-L_{Rx} from Novartis if and when it meets the development, regulatory and sales milestones specified in our agreement. We will share any license fees, milestone payments and royalties equally with Ionis.

Our strategic collaboration with Novartis has a potential aggregate transaction value of over $1.0 billion, plus royalties, which we would generally be required to share equally with Ionis. The calculation of potential aggregate transaction value assumes that Novartis licenses, successfully develops and achieves regulatory approval for both AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} in the U.S., E.U. and Japan, and that Novartis achieves pre-specified sales targets with respect to both drugs. In addition, to the upfront payment that we have received, for AKCEA-APO(a)-L_{Rx} we are eligible to receive up to $675.0 million in milestone payments, including $25.0 million for the achievement of a development milestone, up to $290.0 million for the achievement of regulatory milestones and up to $360.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx} we are eligible to receive up to $530.0 million in milestone payments, including $25.0 million for the achievement of a development milestone, up to $240.0 million for the achievement of regulatory milestones and up to $265.0 million for the achievement of commercialization milestones. We are also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, and Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. We will pay 50% of these license fees, milestone payments and royalties to Ionis as a sublicense fee. See Note 6, *Strategic Collaboration with Novartis*, to our consolidated financial statements for additional information.

We began recognizing revenue under the collaboration with Novartis upon its initiation in 2017. Our collaboration revenue for 2018 was $50.6 million. In addition, we began to recognize TEGSEDI product revenue in 2018 and recognized licensing revenue in the third quarter of 2018 related to our collaboration and license agreement with PTC Therapeutics. Our product revenue and licensing revenue for 2018 was $2.2 million and $12.0 million respectively. Our total revenue for 2018 was $64.9 million. Our net losses have resulted from costs incurred in developing TEGSEDI, WAYLIVRA and the other drugs in our pipeline, preparing to commercialize TEGSEDI and potentially WAYLIVRA upon approval, and general and administrative activities associated with our operations. We expect to continue to generate operating losses and negative operating cash flows for the foreseeable future. The transition to profitability is dependent upon the successful development, approval, and commercialization of our products and product candidates and the achievement of a level of revenue adequate to support our cost structure. We incur meaningful expenses to support commercialization, including manufacturing, marketing, sales and distribution functions. Further, we incur additional costs associated with operating as a public company.

As of December 31, 2018, we had cash, cash equivalents and investments of $252.6 million. We have funded our operating activities through a $100.0 million cash contribution that we received from Ionis in 2015, $75.0 million from initiating our collaboration with Novartis that we received in the first quarter of 2017 and $106.0 million in drawdowns under our line of credit with Ionis that we received in the first and second quarters of 2017. In July 2017, we completed our IPO and raised $182.3 million in net proceeds from the IPO including the $50.0 million Novartis concurrent private placement. In April 2018, we completed a licensing transaction with Ionis to commercialize TEGSEDI. In conjunction with this transaction, Ionis purchased 10.7 million shares of our common stock for $200.0 million. As a result of the MA approval for TEGSEDI in the EU, on August 3, 2018 we issued 1,597,571 shares of our common stock to Ionis as payment of the $40.0 million regulatory milestone for TEGSEDI, and as a result of the regulatory approval for TEGSEDI in the United States, on October 17, 2018 we issued 1,671,849 shares of our common stock to Ionis as payment of the $50.0 million regulatory milestone for TEGSEDI. See Note 7, *License Agreements and Services Agreement with Ionis*, to our consolidated financial statements included in this Form 10-K for more information about our TTR licensing agreement with Ionis. We plan to use our cash, cash equivalents and investments on hand as of December 31, 2018 to further our commercialization efforts of TEGSEDI and WAYLIVRA and continue the advancement of our pipeline drugs.

We expect that our cash, cash equivalents and investments of $252.6 million as of December 31, 2018, together with the receipt of the $150.0 million license fee payment expected in March 2019 as a result of Novartis opt in for the ACKEA-APO(a)-LRx, and cash expected to be generated from sales of TEGSEDI, which has been approved in the U.S., the EU and Canada, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next 12 months from issuance of these financial statements. However, we expect to raise additional funding in the future to continue developing the drugs in our pipeline and to commercialize TEGSEDI, or any other approved drug, including WAYLIVRA. We may seek to obtain additional financing in the future through the issuance of our common stock, through other equity or debt financings or through collaborations or partnerships with other companies. We may not be able to raise additional capital on terms acceptable to us, or at all, and any failure to raise capital as and when needed could compromise our ability to execute on our business plan.

Our Relationship with Ionis

Ionis formed Akcea as a wholly owned subsidiary to complete development of and commercialize Ionis' drugs to treat lipid disorders. We began business operations in January 2015. We licensed our cardiometabolic franchise from Ionis at the beginning of 2015. Prior to licensing these drugs, Ionis' employees performed all of the development, regulatory and manufacturing activities for these drugs either themselves or through third-party providers. As such, Ionis incurred all of the expenses associated with these activities and reported them in its consolidated financial statements. TEGSEDI and AKCEA-TTR-L_{Rx} were licensed from Ionis in April 2018. Prior to then, Ionis had been advancing these drugs in development and incurring the expenses for those activities. Under our license agreements with Ionis, Ionis continued and is continuing to conduct development, regulatory or manufacturing activities for our drugs and to charge us for this work. As of December 31, 2018, Ionis owed approximately 75 percent of our outstanding stock.

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States, or GAAP. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. In the following paragraphs, we describe our most significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results. As described below, there are specific risks associated with these critical accounting policies and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, are as follows:

Revenue Recognition

We began to record revenues from product sales in the fourth quarter of 2018 subsequent to the approval of TEGSEDI in the U.S., EU and Canada. Prior to the fourth quarter of 2018, our revenues were derived from our collaboration agreement with Novartis and collaboration and license agreement with PTC Therapeutics. The terms of such collaboration agreements may include consideration such as nonrefundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services, sales-based milestones and royalties on product sales.

Collaboration and License Revenue

On January 1, 2018, we adopted the new revenue standard, discussed below under Note 2, *Summary of Significant Accounting Policies*, which amended revenue recognition principles and provides a single, comprehensive set of criteria for revenue recognition within and across all industries. Our adoption of the new revenue standard had a material impact on our consolidated financial statements, as discussed below in Note 2. This new revenue standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations, then assess whether each promised good or service is distinct. When we offer options for additional goods or services, such as an option to license a drug in the future or for additional goods or services to be provided in the future, we evaluate whether such options are material rights that should be treated as additional performance obligations. We typically have not concluded that the option to license a drug or the options for additional goods or services that may be requested in the future under our collaboration agreement are material rights as the amounts attributable to such options represent standalone selling price, and therefore no consideration is allocated to these items at the inception of an agreement. When a partner exercises its option to

license a drug or requests the additional goods or services, a new performance obligation is created for that item. Once performance obligations are identified, we then recognize as revenue the amount of the transaction price that we allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time. If the performance obligation is satisfied over time, we recognize revenue based on the use of an output or input method. As of December 31, 2018, we have three revenue streams: our strategic collaboration, option and license agreement, or collaboration agreement, with Novartis Pharma AG, or Novartis, which we entered into in January 2017, our collaboration and license agreement with PTC Therapeutics International Limited, or PTC Therapeutics, which we entered into in August 2018 and commercial product revenue related to sales of TEGESDI in the fourth quarter of 2018. For a complete discussion of the accounting for our revenue streams, see Note 6, *Strategic Collaboration with Novartis*, Note 8, *Collaboration and License Agreement with PTC Therapeutics*, and Note 2, *Summary of Significant Accounting Policies*.

Effective January 1, 2018, we adopted Topic 606 using the full retrospective transition method. Under this method, we revised our consolidated financial statements for prior period amounts including the periods included in this Report on Form 10-K, as if Topic 606 had been effective for such periods. The references "as revised" used herein refer to revisions of amounts originally reported for the year ended December 31, 2017 and as of December 31, 2017 as a result of our adoption of Topic 606.

Impact of Adoption

As a result of adopting Topic 606 on January 1, 2018, we revised our comparative financial statements for the prior years as if Topic 606 had been effective for that period. On September 18, 2018, we filed a Current Report on Form 8-K to present recast consolidated financial statements for each of the three years ended December 31, 2015, 2016 and 2017, to reflect our adoption of the new accounting standard for revenue recognition set forth in Topic 606. The financial information recast in the Form 8-K was originally filed with the SEC in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, which was filed with the SEC on February 28, 2018. Under Topic 605, we recognized revenue from our collaboration with Novartis over time on a straight-line basis. Under Topic 606, we recognize revenue from our collaboration with Novartis using the input method based on the total cost of performing services over time. As a result, the following financial statement line items for fiscal year 2017 were affected.

Consolidated Balance Sheets

	December 31, 2017 (in thousands)		
	As Revised Under Topic 606	As Originally Reported Under Topic 605	Effect of Change
Current portion of deferred revenue	$ 58,192	$ 50,579	$ 7,613
Long-term portion of deferred revenue	12,501	8,306	4,195
Accumulated deficit	$ (296,221)	$ (284,413)	$ (11,808)

Consolidated Statement of Operations and Comprehensive Loss

	Year Ended December 31, 2017 (in thousands, except per share data)		
	As Revised Under Topic 606	As Originally Reported Under Topic 605	Effect of Change
Research and development revenue under collaborative Agreement	$ 43,401	$ 55,209	$ (11,808)
Loss from operations	(120,470)	(108,662)	(11,808)
Net loss	(121,559)	(109,751)	(11,808)
Net loss per share of preferred stock, basic and diluted	(1.80)	(1.55)	(0.25)
Net loss per share of common stock owned by Ionis, basic and diluted	(3.08)	(2.82)	(0.26)
Net loss per share of common stock owned by others, basic and diluted	$ (3.08)	(2.82)	$ (0.26)

Consolidated Statement of Cash Flows

	Years Ended December 31, 2017 (in thousands)		
	As Revised Under Topic 606	As Originally Reported Under Topic 605	Effect of Change
Net loss	$ (121,559)	$ (109,751)	$ (11,808)
Adjustments to reconcile net loss to net cash used in operating activities:			
Deferred revenue	70,693	58,885	11,808
Cash, cash equivalents and restricted cash at beginning of period	7,857	7,857	—
Cash, cash equivalents and restricted at end of period	$ 58,367	$ 58,367	$ —

Product Revenue, Net

Subsequent to regulatory approval in Europe on July 11, 2018 and FDA approval in the U.S. on October 5, 2018, in the fourth quarter of 2018 we began to sell TEGSEDI in the U.S. and Germany. In the U.S., the product is distributed through an exclusive distribution agreement with a third-party logistics (3PL) company that takes title to the product and represents our sole customer in the U.S. Our U.S. customer distributes TEGSEDI to a specialty pharmacy and a specialty distributor (collectively referred to as "wholesalers"), who then distribute the product to health care providers and patients. In Germany, the product is distributed through a non-exclusive distribution model with a 3PL that takes title to the product and currently represents our sole customer in Germany. Our customer in Germany then distributes TEGSEDI to hospitals and pharmacies in Germany.

Revenue from product sales are recognized when the customer obtains control of our product, which occurs at a point in time, upon transfer of title to the customer. We record shipping and handling costs within cost of goods sold on our consolidated statement of operations. We classify payments to customers or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative expenses in our consolidated statements of operations. Otherwise payments to customers or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. Taxes collected from customers relating to product sales and remitted to governmental authorities are excluded from revenue. We have elected not to adjust consideration for the effects of a significant financing component when the period between the transfer of a promised good or service to the customer and when the customer pays for that good or service will be one year or less. Our payment terms are generally between thirty to ninety days. We expense incremental costs of obtaining a contract as and when incurred since the expected amortization period of the asset that we would have recognized is one year or less.

Reserves for Variable Consideration

Revenues from product sales are recorded at the net sales price (transaction price), which includes estimates of variable consideration for which reserves are established and which result from discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that are offered within contracts between us and our customers, wholesalers, health care providers and other indirect customers relating to the sale of TEGSEDI. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than a customer). Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is considered probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

The following are the components of variable consideration related to product revenue:

Chargebacks: In the U.S., we estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to our U.S. customer. Our U.S. customer charges us for the difference between what they pay for the product and the selling price to the qualified healthcare providers. We record reserves for these chargebacks related to product sold to our U.S. customer during the reporting period, as well as our estimate of product that remains in the distribution channel at the end of the reporting period that we expect will be sold to qualified healthcare providers in future periods.

Government rebates: We are subject to discount obligations under government programs, including Medicaid programs and Medicare in the United States. We estimate Medicaid and Medicare rebates based upon a range of possible outcomes that are probability-weighted for the estimated payer mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a liability that is included in accrued expenses on our consolidated balance sheet. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments. In Germany, pharmaceutical companies must grant a specified rebate percentage to the German government. We have included this rebate as a reduction of revenue in the period the related product revenue is recognized.

Trade discounts and allowances: We provide customary invoice discounts on TEGSEDI sales to our U.S. customer for prompt payment that are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we receive and pay for various distribution services from our U.S. customer and wholesalers in the U.S. distribution channel. For services that are either not distinct from the sale of our product or for which we cannot reasonably estimate the fair value, such fees are classified as a reduction of product revenue.

Product Returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the product's expiration date. We estimate the amount of product sales that may be returned and record the estimate as a reduction of revenue and a refund liability in the period the related product revenue is recognized. Based on the distribution model for TEGSEDI, contractual inventory limits with our customer and wholesalers and the price of TEGSEDI, we believe there will be minimal returns. Our customer in Germany only takes title to the product once it receives an order from a hospital or pharmacy and therefore does not maintain any inventory of TEGSEDI. Therefore, there is limited return risk and the Company has not recorded any return estimate in the transaction price for TEGSEDI sold in Germany.

Other incentives: In the U.S., other incentives include co-payment assistance we provide to patients with commercial insurance that have coverage and reside in states that allow co-payment assistance. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that we expect to receive associated with product that has been recognized as revenue. The estimate is recorded as a reduction of revenue in the same period the related revenue is recognized.

During the year ended December 31, 2018, we recorded product revenue, net, of $2.2 million, which consist of $1.2 million of TEGSEDI sales in the U.S., and $1.0 million of TEGSEDI sales in Germany. The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the year ended December 31, 2018 (in thousands):

	Chargebacks, discounts and fees	Government and other rebates	Returns	Total
Balance at December 31, 2017	$ —	$ —	$ —	$ —
Provision related to current period sales	50	293	5	348
Adjustment related to prior period sales	—	—	—	—
Credit or payments made during the period	—	—	—	—
Balance at December 31, 2018	$ 50	$ 293	$ 5	$ 348

Inventory

Prior to the regulatory approval of our product candidates, we incur expenses for the manufacturing of drug product that could potentially be available to support the commercial launch of our products. Until the first reporting period when regulatory approval has been received or is otherwise considered probable, we record all such costs as research and development expense.

For inventory related costs incurred subsequent to July 1, 2018, we reflected these amounts as inventory on our consolidated balance sheets at the lower of cost or market value under the first-in, first-out, or FIFO, basis. We periodically analyze our inventory levels, and write down inventory that has become obsolete, inventory that has a cost basis in excess of its estimated realizable value and inventory in excess of expected sales requirements as cost of product sales. The determination of whether inventory costs will be realizable requires estimates by our management and if actual market conditions are less favorable than projected by our management, additional write-downs of inventory may be required which would be recorded as a cost of product sales in the consolidated statements of operations.

At December 31, 2018 a majority of our physical inventory for TEGSEDI was produced prior to when we obtained regulatory approval and accordingly had no cost basis as we recorded the related costs as research and development expense in prior periods. At December 31, 2018 the amount of finished goods recorded in our consolidated balance sheets in other current assets related to our approved product TEGSEDI was $85,000.

Intangible Assets

We obtained exclusive licenses from Ionis for specific patents that Ionis owns and maintains related to our drug pipeline. We recorded our licenses from Ionis as a capital contribution using the carryover basis of Ionis' historical cost for the related patents. We are amortizing our capitalized licenses over their estimated useful life, which is the term of the underlying individual patents owned by Ionis.

In addition, we maintain definite-lived intangible assets related to regulatory milestone payments made to Ionis that are recoverable through future cash flows from approved products, which are capitalized as license intangible assets. These assets are amortized over their remaining useful lives, which are generally estimated to be the remaining patent life. If our estimate of the product’s useful life is shorter than the remaining patent life, then the shorter period is used. Intangible assets are amortized using the economic consumption method if anticipated future revenue can be reasonably estimated. The straight-line method is used when future revenue cannot be reasonably estimated. Amortization expense is recorded as a component of cost of sales to the extent the underlying license is commercialized or research and development prior to its commercialization in the consolidated statements of operations.

Cost of Product Sales

As a result of receiving marketing authorization, or MA, approval for TEGSEDI from the European Commission, or EC, in July 2018, we began recording all TEGSEDI related expenses as cost of product sales starting in July 2018. Cost of product sales consists of manufacturing costs, transportation and freight, and indirect overhead costs associated with the manufacturing and distribution of TEGSEDI. Cost of product sales may also include period costs related to certain manufacturing services and inventory adjustment charges. Additionally, we expensed a significant portion of the cost of producing TEGSEDI that we will use in the commercial launch as research and development expense prior to the regulatory approval of TEGSEDI.

Estimated Liability for Research and Development Costs

We record accrued liabilities related to expenses for which vendors or service providers have not yet billed us. These liabilities are for products or services that we have received and primarily relate to ongoing nonclinical and clinical studies. These costs primarily include third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have drugs in concurrent nonclinical and clinical studies at several sites throughout the world. To ensure that we have adequately provided for ongoing nonclinical and clinical research and development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

Stock-Based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our employee stock purchase plan, or ESPP, based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise the expense in subsequent periods if actual forfeitures differ from those estimates.

We value our stock option awards and stock purchase rights under our ESPP using the Black-Scholes model. The determination of the grant date fair value of options using an option pricing model is affected principally by our estimated common stock fair value and requires us to make a number of other assumptions, including: the expected life of the option, the volatility of the underlying stock, the risk-free interest rate and expected dividends.

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted vest annually over a four-year period.

Prior to December 2015, Ionis granted our employees options to purchase shares of Ionis' common stock, or Ionis options. In December 2015, we granted our employees holding Ionis options additional options to purchase shares of our common stock, or Akcea options.

We determined the stock-based compensation expense for the Ionis options at the date of grant and recognized compensation expense over the vesting period of the Ionis options. In December 2015, we accounted for the issuance of the Akcea options as a modification to the original grant of the Ionis options because the grant of the Ionis options and Akcea options essentially represented a single stock award as the exercisability provisions of the Ionis options and Akcea options grants were interrelated and mutually exclusive. The total compensation expense measured on the modification date was the sum of the grant date fair value of the Ionis options plus any incremental compensation cost resulting from the grant of the Akcea options.

In 2016, we began concurrently granting Ionis options and Akcea options to our employees. Because the exercisability provisions of the awards are interrelated and mutually exclusive as described above, the fair values of the Ionis options and the Akcea options were determined on the date of grant and the option with the greater fair value was recognized over the vesting period of the awards. In 2017, we no longer concurrently granted Ionis and Akcea options. Our board of directors only receive grants under the Akcea option plan.

Following our IPO, we no longer grant Ionis options to our employees. Under the terms of the Ionis options, when we completed our IPO, the Ionis options our employees were holding were terminated. The termination of the Ionis options was determined not to be a modification, as the options were terminated based upon the existing contractual terms of the option agreements. As such, we will continue to recognize expense based on the valuation that was determined upon the grant date for options issued in 2016 or the modification date for options issued in 2015 and 2017.

The fair value of stock options granted under our 2015 Equity Incentive Plan is based on the fair value of our common stock on the date of grant. The fair value of stock options granted under the Ionis 2011 Equity Incentive Plan is based on the fair value of Ionis' common stock on the date of grant. Options granted to employees vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of ten years. Options granted to directors vest annually over a four-year period and have a term of ten years.

See Note 9, *Equity and Stock-based Compensation,* for additional information regarding our stock-based compensation plans.

Income Taxes

Prior to the completion of our IPO we filed our tax returns on a consolidated and combined basis with Ionis for federal and state income tax purposes, respectively. For financial statement purposes when we are required to file on a consolidated or combined basis, we calculate our income tax amounts, including net operating losses and tax credit carryforwards, using a separate return methodology which determines income taxes as if we were a separate taxpayer from Ionis. Effective July 19, 2017, the date of our IPO, we are no longer included in the consolidated federal income tax return with Ionis. We determined the amount of federal tax attributes, primarily net operating losses and tax credit carryforwards that transferred to us upon deconsolidation from Ionis. We are still required to file most of our state tax returns on a consolidated or combined basis with Ionis. Therefore, for financial statement purposes we calculated our state income tax amounts using the separate return method.

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in our financial statements or tax returns. In addition, deferred tax assets are recorded for the future benefit of utilizing net operating losses and research and development credit carry forwards. Valuation allowances are provided when necessary to reduce deferred tax assets to the amount expected to be realized.

We apply the authoritative accounting guidance prescribing a threshold and measurement attribute for the financial recognition and measurement of a tax position taken or expected to be taken in a tax return. We recognize liabilities for uncertain tax positions based on a two-step process. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained on audit, including resolution of related appeals or litigation settlement. The second step is to estimate and measure the tax benefit as the largest amount that is more than 50% likely to be realized upon ultimate settlement.

We recognize interest and penalties related to unrecognized tax benefits within the income tax expense line in the accompanying consolidated statements of operations. Accrued interest and penalties are included within other long-term liabilities in the consolidated balance sheets.

Significant judgment is required in evaluating our uncertain tax positions and determining our provision for income taxes. Although we believe our reserves are reasonable, no assurance can be given that the final tax outcome of these matters will not be different from that which is reflected in our historical income tax provisions and accruals. We adjust these reserves for changing facts and circumstances, such as the closing of a tax audit or the refinement of an estimate. To the extent that the final tax outcome of these matters is different than the amounts recorded, such differences may impact the provision for income taxes in the period in which such determination is made.

Significant judgment is also required in determining any valuation allowance recorded against deferred tax assets. In assessing the need for a valuation allowance, we consider all available evidence, including scheduled reversal of deferred tax liabilities, past operating results, the feasibility of tax planning strategies and estimates of future taxable income. Estimates of future taxable income are based on assumptions that are consistent with our plans. Assumptions represent management's best estimates and involve inherent uncertainties and the application of management's judgment. Should actual amounts differ from our estimates, the amount of our tax expense and liabilities could be materially impacted.

We record a valuation allowance to reduce the balance of our net deferred tax assets to the amount we believe is more-likely-than-not to be realized. We have incurred financial statement losses since inception and as a result we have a full valuation allowance recorded against our net deferred tax assets. We regularly assess the future realization of our net deferred tax assets and will reduce the valuation allowance in any such period in which we determine that all, or a portion, of our deferred tax assets are more-likely-than-not to be realized.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries. The earnings of non-U.S. subsidiaries are currently expected to be indefinitely reinvested in non-U.S. operations.

Results of Operations

In order to analyze and compare our results of operations to other similar companies, we believe it is important to exclude non-cash stock-based compensation expense related to equity awards from our expenses. We believe non-cash stock-based compensation expense is not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding it. All numbers presented below exclude stock-based compensation expense unless otherwise indicated.

Comparison of the Years Ended December 31, 2018 and 2017 (as revised)

Revenue

The following table sets forth our revenue for the periods presented (in thousands):

	Years Ended December 31,	
	2018	2017 (as revised)
Product revenue	$ 2,237	$ —
Licensing revenue	12,000	—
Research and development revenue under collaboration agreement	50,630	43,401
Total revenue	$ 64,867	$ 43,401

Product revenue. Product revenue of $2.2 million for 2018 relates to sales of TEGSEDI in the Unites States and Germany. For the year ended December 31, 2017, we did not generate any product revenue.

Licensing revenue. Licensing revenue of $12.0 million for 2018 relates to the upfront payment received from PTC Therapeutics related to our PTC License Agreement entered into in August 2018. For the year ended December 31, 2017, we did not generate any licensing revenue.

Research and development revenue. In 2018, we recognized $50.6 million compared to $43.4 million in 2017 (as revised), in research and development revenue from our collaboration with Novartis. The increase in research and development revenue is primarily the result of level of efforts related to activities for our AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} programs.

Cost of sales and license expense

The following table sets forth our cost of sales and license expense for the periods presented (in thousands):

	Years Ended December 31,	
	2018	2017
Cost of sales - product	$ 1,660	$ —
Cost of sales - intangible asset amortization	2,713	—
Cost of license	7,200	—
Total cost of sales and license expenses, excluding non-cash stock-based compensation expense	11,573	—
Non-cash stock-based compensation expense	160	—
Total cost of sales and license expenses	$ 11,733	$ —

Cost of sales – product expense of $1.7 million for 2018 consists of period costs and certain fixed costs associated with the manufacturing of TEGSEDI. We do not expect fixed costs will increase in direct correlation to sales. Based on our policy, we expense costs associated with the manufacture of our products as research and development prior to regulatory approval. Certain product costs of TEGSEDI units recognized as revenue during the year ended December 31, 2018 were incurred prior to the July 2018 EU approval, and therefore are not included in cost of sales during the year. We expect cost of sales to increase as we deplete these inventories. The cost of units sold during the period for which there was no cost basis was $0.1 million for the year ended December 31, 2018. No product cost of sales was recorded for the year ended December 31, 2017. All amounts exclude non-cash compensation expense related to equity awards.

Cost of sales expense – intangible asset amortization of $2.7 million for 2018 consist of amortization of intangible assets recorded as a result of the achievement of TEGSEDI regulatory milestones in the U.S. and E.U. All amounts exclude non-cash compensation expense related to equity awards.

Cost of license of $7.2 million for 2018 consists of TTR sub-license expense due to Ionis related to the payment received as part of the licensing agreement entered into with PTC Therapeutics in August 2018. No license cost of sales was recorded for the year ended December 31, 2017. All amounts exclude non-cash compensation expense related to equity awards.

Research and development expense

The following table sets forth our research and development expenses for the periods presented (in thousands):

	Years Ended December 31,	
	2018	2017
External TEGSEDI expenses	26,044	—
External WAYLIVRA expenses	22,246	26,505
Other external research and development projects expenses	40,560	21,789
Research and development personnel and overhead expenses	32,055	21,572
Sublicensing expenses	—	48,394
Total research and development expenses, excluding non-cash stock-based compensation expense	120,905	118,260
Non-cash stock-based compensation expense	9,435	8,630
Total research and development expenses	$ 130,340	$ 126,890

Research and development expenses were $120.9 million for the year 2018 compared to $118.3 million for the same period in 2017. The slight increase in research and development expenses was primarily due to development activities related to TEGSEDI, development activities related to our Phase 2b studies for AKCEA APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx} which were initiated in the first quarter of 2018 and personnel and overhead expense to support our development efforts. This increase was offset primarily due to sublicensing expenses related to our collaboration with Novartis, which we incurred in the first quarter of 2017, the majority of which were non-cash, a decrease in development activities for AKCEA APO(a)-L_{Rx} as the clinical study ended, finished data collection and reported topline results, as well as a decrease in development activities for WAYLIVRA. All amounts exclude non-cash compensation expense related to equity awards.

Selling, general and administrative expense

The following table sets forth our selling, general and administrative expenses for the periods presented (in thousands):

	Years Ended December 31,	
	2018	2017
Selling, general and administrative expenses	$ 118,923	$ 28,072
Non-cash compensation expense related to equity awards	34,687	8,909
Total Selling, general and administrative expenses	$ 153,610	$ 36,981

Selling, general and administrative expenses were $118.9 million for 2018 compared to $28.1 million for the same period in 2017. Our selling, general and administrative expenses increased due to the ongoing buildout of our commercial organization and advancement of pre-commercialization and commercialization activities necessary to launch TEGSEDI in the U.S., the EU and Canada, and WAYLIVRA, if approved for marketing in the EU. All amounts exclude non-cash compensation expense related to equity awards.

Other income and other expense

Investment income. Investment income for 2018 totaled $5.7 million compared to $1.8 million for the same period in 2017. The increase in investment income was primarily due to a higher average investment balance and an increase in the interest rates on high quality debt and U.S. government agencies investments during 2018 compared to 2017.

Interest expense. Interest expense is comprised entirely of interest incurred under our line of credit agreement with Ionis. We incurred no interest expense during 2018. Interest expense for 2017 totaled $1.7 million. The outstanding principal and accrued interest under our line of credit converted into 13,438,339 shares of our common stock in connection with the closing of our IPO in July 2017 and we no longer have access to this line of credit following the closing of our IPO.

Net Loss and Net Loss Per Share

Net loss for 2018 was $225.8 million compared to $121.6 million for the same period in 2017 (as revised). We incurred a higher net loss during 2018 compared to 2017 primarily due to the development and pre-commercialization and commercial activities for TEGSEDI, the increase in expenses related to pre-commercialization and development activities for WAYLIVRA and our other drugs, and the ongoing global expansion of our company. Basic and diluted net loss per preferred share for the year ended December 31, 2017 (as revised) was $1.80. We had no outstanding preferred shares at December 31, 2018. Basic and diluted net loss per common share owned by Ionis and owned by others for the year ended December 31, 2018 was $2.74 and $2.87, respectively. Basic and diluted net loss per common share owned by Ionis and owned by others for the year ended December 31, 2017 (as revised) was $3.08.

Comparison of the Years Ended December 31, 2017 (as revised) and 2016

Revenue

For the year ended December 31, 2017, we recognized $43.4 million in research and development revenue (as revised) from our collaboration with Novartis, which we initiated in January 2017. For the year ended December 31, 2016, we did not generate any revenue**.**

Research and development expense

The following table sets forth our research and development expenses for the periods presented (in thousands):

	Years Ended December 31,	
	2017	2016
External WAYLIVRA expenses	$ 26,505	$ 38,403
Other external research and development projects expenses	21,789	11,567
Research and development personnel and overhead expenses	21,572	13,913
Sublicensing expenses	48,394	—
Total research and development expenses, excluding non-cash stock-based compensation expense	118,260	63,883
Non-cash stock-based compensation expense	8,630	4,576
Total research and development expenses	$ 126,890	$ 68,459

Research and development expenses were $118.3 million for 2017 and increased compared to $63.9 million for 2016. The increase in expenses was primarily due to sublicensing expenses related to our collaboration with Novartis, which we incurred in the first quarter of 2017, the majority of which were non-cash. The progression of our other drugs in development, including AKCEA-APO(a)-L_{Rx}, AKCEA-APOCIII-L_{Rx} and AKCEA-ANGPTL3-L_{Rx}, during 2017 also contributed to the increase in our expenses. In particular we commenced four Phase 2 trials in 2017. This increase in research and development expenses was offset in part by a decrease in external WAYLIVRA expenses primarily related to the completion of the phase 3 program. All amounts exclude non-cash compensation expense related to equity awards.

Selling, general and administrative expense

The following table sets forth our selling, general and administrative expenses for the periods presented (in thousands):

	Years Ended December 31,	
	2017	2016
Selling, general and administrative expenses	$ 28,072	$ 9,480
Non-cash compensation expense related to equity awards	8,909	5,573
Total Selling, general and administrative expenses	$ 36,981	$ 15,053

Selling, general and administrative expenses were $28.1 million for 2017 and increased compared to $9.5 million for 2016. Our general and administrative expenses increased due to the ongoing buildout of our commercial organization and advancement of pre-commercialization activities necessary to launch WAYLIVRA, if approved for marketing in the US, Canada and certain EU countries. All amounts exclude non-cash compensation expense related to equity awards.

Other income and other expense

Investment income. Investment income for 2017 totaled $1.8 million compared to $0.3 million for 2016. The increase in investment income was primarily due to a higher average short-term investment balance and an increase in the interest rates on high quality debt and U.S. government agencies investments during 2017 compared to 2016.

Interest expense. Interest expense is comprised entirely of interest incurred under our line of credit agreement with Ionis. Interest expense for 2017 totaled $1.7 million. We incurred no interest expense for 2016. The outstanding principal and accrued interest under our line of credit converted into 13,438,339 shares of our common stock in connection with the closing of our IPO in July 2017 and we no longer have access to this line of credit following the closing of our IPO.

Net Loss and Net Loss Per Share

Net loss for 2017 (as revised) was $121.6 million compared to $83.2 million for 2016. Basic and diluted net loss per preferred share for the year ended December 31, 2017 (as revised) was $1.80 compared to $2.88 for 2016. Basic and diluted net loss per common share owned by Ionis and owned by others for the year ended December 31, 2017 (as revised) was $3.08. We had no outstanding common stock at December 31, 2016. We incurred a higher net loss in 2017 compared to 2016 primarily due to the increase in expenses related to pre-commercialization and development activities for our drugs, sublicensing expenses related to our collaboration with Novartis, the ongoing global expansion of our company and becoming and operating as a public company.

Liquidity and Capital Resources

At December 31, 2018, we had cash, cash equivalents and investments of $252.6 million and accumulated deficit of $522.0 million.

We have funded our operating activities through a $100.0 million cash contribution that we received from Ionis in 2015, $75.0 million from initiating our collaboration with Novartis that we received in the first quarter of 2017 and $106.0 million in drawdowns under our line of credit with Ionis that we received in the first and second quarters of 2017. Our borrowings under our line of credit agreement with Ionis converted into shares of our common stock at the IPO price in connection with the closing of our IPO in July 2017. We no longer have access to the line of credit. Additionally, in July 2017 we received $182.3 million in net proceeds from our IPO, including $25.0 million Ionis invested in our IPO and the Novartis concurrent private placement of $50.0 million.

In April 2018, the stockholders other than Ionis and its affiliates approved the development, commercialization, collaboration and license agreement, or TTR License Agreement, pursuant to which we acquired an exclusive license from Ionis to TEGSEDI and AKCEA-TTR-L_{Rx} and a stock purchase agreement, or Ionis SPA, with Ionis, our majority shareholder, which we entered into on March 14, 2018. To support our commercialization of TEGSEDI and AKCEA-TTR-L_{Rx}, Ionis purchased 10.7 million shares of our common stock for $200.0 million.

At December 31, 2018, we had working capital of $186.5 million compared to working capital of $178.4 million at December 31, 2017. Working capital increased in 2018 primarily due to the increase in our cash, cash equivalents and investments as a result of our financing activities. This increase is offset by activities related to our normal course of business. As of December 31, 2018, our outstanding payable to Ionis was $18.9 million under our Amended Services Agreement with Ionis

TEGSEDI is approved in the U.S., E.U. and Canada and we are now beginning our commercialization efforts in these three regions. We began to generate product revenue from TEGSEDI drug sales in the fourth quarter of 2018. We anticipate that we will continue to incur losses for the foreseeable future, and losses may continue to increase as we develop, seek regulatory approval for, and begin to commercialize our other pipeline drugs. We are subject to all of the risks incident in developing and commercializing new drugs and we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business.

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} as part of our strategic collaboration with Novartis discussed in Note 6, *Strategic Collaboration with Novartis*. As a result we earned a license fee of $150.0 million of which we will pay $75.0 million to Ionis as a sublicense fee. We will issue 2,837,373 shares of our common stock to Ionis as payment of the $75.0 million sublicense fee.

Future Funding Requirements

We expect to raise additional funding in the future to continue developing the drugs in our pipeline and to expand our commercial efforts for TEGSEDI, which has been approved in the U.S., E.U. and Canada, and WAYLIVRA, for which we are in on going regulatory discussion in those same jurisdictions. We expect that our cash, cash equivalents and investments of $252.6 million as of December 31, 2018, together with the receipt of the $150.0 million license fee payment expected in March 2019 as a result of Novartis opt in for the ACKEA-APO(a)-LRx, and cash expected to be generated from sales of TEGSEDI, which has been approved in the U.S., the EU and Canada, will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next 12 months from issuance of these financial statements. Until such time, if ever, as we can generate substantial product revenue, we may finance our cash needs through additional financing in the future through the issuance of our common stock, through other equity or debt financings or through collaborations or partnerships with other companies. In any event, we may not generate significant revenue from product sales prior to the use of our existing cash, cash equivalents and investments. We do not have any committed external source of funds. Additional capital may not be available on reasonable terms, if at all. To the extent that we raise additional capital through the sale of stock or convertible debt securities, the ownership interest of our stockholders will be diluted and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include increased fixed payment obligations and covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, declaring dividends, selling or licensing intellectual property rights and other operating restrictions that could adversely affect our ability to conduct our business. If we raise additional funds through collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to our drugs or grant licenses on terms that may not be favorable to us. If we cannot raise additional funds through stock offerings 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 commercialize our drugs even if we would otherwise prefer to develop and commercialize the drugs ourselves.

Our forecast of the period of time through which our financial resources will be adequate to support our operations involves risks and uncertainties, and actual results could vary as a result of a number of factors. We have based this estimate on assumptions that may prove to be wrong and we could use our available capital resources sooner than we currently expect. The amount and timing of future funding requirements, both near- and long-term, will depend on many factors, including, but not limited to:

- the design, initiation, progress, size, timing, costs and results of our clinical and nonclinical studies;
- the outcome, timing and cost of regulatory approvals by the FDA and comparable foreign regulatory authorities, including the potential for the FDA or comparable foreign regulatory authorities to require that we perform more studies than, or evaluate clinical endpoints other than, those that we currently expect;
- the number and characteristics of drugs that we may pursue;
- our need to expand our development activities, including our need and ability to hire additional employees;
- the effect of competing technological and market developments;
- the cost of establishing sales, marketing, manufacturing and distribution capabilities for our drugs;
- our strategic collaborators' success in developing and commercializing our drugs;
- our need to add infrastructure, implement internal systems and hire additional employees to operate as a public company; and
- the revenue, if any, generated from commercial sales of our drugs for which we receive marketing authorization, which may be affected by market conditions, including obtaining coverage and adequate reimbursement of our drugs from third-party payors, including government programs and managed care organizations, and competition within the therapeutic class to which our drugs are assigned.

If we cannot expand our operations or otherwise capitalize on our business opportunities because we lack sufficient capital, our business, financial condition and results of operations could be materially adversely affected.

Contractual Obligations and Commitments

	Payments due by period				
Year Ending December 31,	**Total**	**Less than 1 year**	**1 to 3 years**	**3 to 5 years**	**More than 5 years**
Operating lease obligations	$ 23,688	$ 2,308	$ 4,711	$ 4,805	$ 11,864
Purchase commitments	5,033	5,033	—	—	—
Total	$ 28,721	$ 7,341	$ 4,711	$ 4,805	$ 11,864

Operating Lease

On April 5, 2018, we entered into an operating lease agreement with MEPT Seaport 13 Stillings LLC, or MEPT, for 30,175 square feet of office space located in Boston, Massachusetts for our new corporate headquarters. The commencement date of the lease was August 2018 and the initial term of the lease is 123 months with one five-year renewal option. We took occupancy of the office space in Boston, Massachusetts in September 2018. MEPT is providing us with a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. We provided MEPT with a letter of credit to secure our obligations under the lease in the initial amount of $2.4 million, to be reduced to $1.8 million on the third anniversary of the rent commencement date and to $1.2 million on the fifth anniversary of the rent commencement date if we meet certain conditions set forth in the lease at each such time. This balance is included in deposits and other assets on the accompanying consolidated balance sheets.

On November 12, 2018, we entered into an operating lease agreement with Ionis Pharmaceuticals to sublease 4,723 square feet of office space located in Carlsbad, California. The commencement date was March 2018 and the term of the lease is 64 months with a four-month free rent period.

Rent expense for the year ended December 31, 2018, 2017 and 2016 was $2.4 million, $0.7 million and $0.4 million, respectively. We recognize rent expense on a straight-line basis over the lease term for the lease of our office spaces, which resulted in a deferred rent balance of $4.8 million and $39,000 at December 31, 2018 and 2017, respectively.

Purchase Commitments

Purchase commitments include agreements to purchase goods or services that are enforceable and legally binding on us and that specify all significant terms, including, fixed or minimum quantities to be purchased; fixed, minimum or variable price provisions; and the approximate timing of the transaction. Such obligations are related principally to inventory purchase orders based on our current manufacturing needs and require significant lead times to be fulfilled by our vendors. Purchase commitments exclude agreements that are cancelable without penalty

License Fee Payment

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} as part of our strategic collaboration with Novartis discussed in Note 6, *Strategic Collaboration with Novartis* to our consolidated financial statements included in this Form 10-K. As a result we earned a license fee of $150.0 million of which we will pay $75.0 million to Ionis as a sublicense fee. We will issue 2,837,373 shares of our common stock to Ionis as payment of the $75.0 million sublicense fee.

Recently Issued Accounting Pronouncements

We describe the recently issued accounting pronouncements that apply to us in Note 2, *Summary of Significant Accounting Policies*, to our consolidated financial statements.

Off-balance Sheet Arrangements

We did not have any off-balance sheet arrangements during the period presented, as defined in the rules and regulations of the SEC.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Interest Rate Risk

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We place our cash equivalents and short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations, and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or Fitch, respectively. We have established guidelines relative to diversification and maturities that are designed to maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

Foreign Exchange Risk

Our results of operations are subject to foreign currency exchange rate fluctuations as we have foreign subsidiaries, Akcea Therapeutics UK Ltd., or Akcea UK, Akcea Therapeutics Canada, Inc., or Akcea Canada, Akcea Therapeutics France SAS, , or Akcea France, Akcea Therapeutics Germany GmbH, or Akcea Germany, and Akcea Therapeutics Ireland Limited, or Akcea Ireland with functional currencies other than the U.S. dollar. We created these foreign subsidiaries to support our initial pre-commercialization activities in North America and Europe and to serve as potential entities for future North American and European operations. We translate the foreign subsidiaries' functional currencies to our reporting currency, the U.S. dollar. As a result, our financial position, results of operations and cash flows can be affected by market fluctuations in the foreign currencies to U.S. dollar exchange rate which are difficult to predict. However, because the Akcea foreign subsidiaries currently have limited operations, the effect of fluctuations of the foreign currencies to U.S. dollar exchange rate on our consolidated results is immaterial to our consolidated financial statements. Our business strategy incorporates potentially significant international expansion, particularly in anticipation of approval of WAYLIVRA, therefore we expect that the impact of foreign currency exchange rate fluctuations may become more substantial in the future.

Item 8. Financial Statements and Supplementary Data

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a) (1) and (2), and incorporate them herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or Exchange Act) that are designed to ensure that information we are required to disclose in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC’s rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. We designed and evaluate our disclosure controls and procedures recognizing that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance and not absolute assurance of achieving the desired control objectives.

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of December 31, 2018.

Management’s Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting for our company. Internal control over financial reporting is defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officer and effected by the company's board of preparation of financial statements for external purposes in accordance with GAAP and directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the includes those policies and procedures that: (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of our company's assets that could have a material effect on the financial statements.

Internal control over financial reporting is designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements prepared for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, with the participation of our principal executive and principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2018, based on criteria for effective internal control over financial reporting established in Internal Control—Integrated Framework (2013), issued by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO. Based on its assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2018, based on those criteria.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to the deferral allowed under the JOBS Act for emerging growth companies

Changes in Internal Control Over Financial Reporting

The above assessment did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and 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

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption "ELECTION OF DIRECTORS," including in particular the information under "Nominating, Governance and Review Committee" and "Audit Committee," contained in our definitive information statement (the "Information Statement"), to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics and Business Conduct" contained in the Information Statement. Our Code of Ethics and Business Conduct is posted on our website at www.akceatx.com(1) and is available in print free of charge to any stockholder upon request. We intend to disclose future amendments to, or waivers from, our Code of Ethics and Business Conduct on our website. No such waivers have been issued during fiscal 2017.

Item 1, Part I of this Report contains information concerning our executive officers. We incorporate by reference the information required by this Item concerning compliance with Section 16(a) of the Exchange Act from the information under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Information Statement to be filed within 120 days after the end of the fiscal year ended December 31, 2018.

(1) Any information that is included on or linked to our website is not part of this Form 10-K.

Item 11. Executive Compensation

We incorporate by reference the information required by this item to the information under the caption "EXECUTIVE COMPENSATION," "Compensation Committee Interlocks and Insider Participation" and "COMPENSATION COMMITTEE REPORT" contained in the Information Statement to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

We incorporate by reference the information required by this item to the information under the caption "SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT" contained in the Information Statement to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

Securities Authorized for Issuance under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2018.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance	
Equity compensation plans approved by stockholders (a)	11,010,828	$ 15.00	2,578,939	(b)
Total	11,010,828	$ 15.00	2,578,939	

(a) Consists of two Akcea plans: 2015 Equity Incentive Plan and 2017 Employee Stock Purchase Plan, or ESPP.

(b) Of these shares, 968,449 remained available for purchase under the ESPP as of December 31, 2018. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year, we automatically increase the aggregate number of shares reserved for issuance under the plan by an amount equal to the lesser of (i) 1% of the total number of shares of Common Stock outstanding on December 31st of the preceding calendar year, and (ii) 500,000 shares of Common Stock shares.

Item 13. Certain Relationships and Related Transactions, and Director Independence

We incorporate by reference the information required by this item to the information under the captions "Independence of the Board of Directors" and "Certain Relationships and Related Transactions" contained in the Information Statement to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

Item 14. Principal Accounting Fees and Services

We incorporate by reference the information required by this item to the information under the caption "Ratification of Selection of Independent Auditors" contained in the Information Statement to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

Part IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

Item 16. Form 10-K Summary

Not Applicable.

Index to EXHIBITS

Exhibit	Description	Incorporated by Reference			
		Schedule / Form	File Number	Exhibit	File Date
3.1	Amended and Restated Certificate of Incorporation of the Registrant	8-K	001-38137	3.1	July 19, 2017
3.2	First Amendment to Amended and Restated Certificate of incorporation of the Registrant	8-K	001-38137	3.1	April 17, 2018
3.3	Second Amendment to Amended and Restated Certificate of Incorporation of the Registrant	10-Q	001-38137	3.1	May 7, 2018
3.4	Amended and Restated Bylaws of the Registrant	8-K	001-38137	3.2	July 19, 2017
4.1	Reference is made to Exhibits 3.1, 3.2, 3.3 and 3.4				
4.2	Form of Common Stock Certificate of the Registrant	S-1	333-216949	4.1	June 20, 2017
4.3	Amended and Restated Investor Rights Agreement by and among the Registrant and Ionis Pharmaceuticals, Inc., dated March 14, 2018	8-K	001-38137	4.1	March 15, 2018
4.4	Form of Indenture, between the Registrant and one or more trustees to be named	S-3	333-227403	4.4	September 18, 2018
10.1#	Collaboration and License Agreement by and among the Registrant and PTC Therapeutics International Limited, dated August 1, 2018	10-Q	001-38137	10.1	November 6, 2018
10.2	Operating Lease Agreement by and among Registrant and MEPT Seaport 13 Stillings LLC, dated April 5, 2018	10-Q	001-38137	10.1	August 7, 2018
10.3*	Operating Sublease Agreement by and among Registrant and Ionis Pharmaceuticals, Inc., dated November 12, 2018				
10.4†	Form of Indemnity Agreement	S-1	333-216949	10.1	April 10, 2017
10.5†	2015 Equity Incentive Plan, as amended, and Form of Award Agreement	8-K	001-38137	10.1	November 23, 2018
10.6†	2017 Employee Stock Purchase Plan	S-1	333-216949	10.3	June 20, 2017
10.7#	Development, Commercialization and License Agreement by and among Registrant and Ionis Pharmaceuticals, Inc., dated December 18, 2015	S-1	333-216949	10.4	March 27, 2017
10.8#	Services Agreement by and among Registrant and Ionis Pharmaceuticals, Inc., dated December 18, 2015	S-1	333-216949	10.5	March 27, 2017
10.9	Senior Unsecured Line of Credit by and among Registrant and Ionis Pharmaceuticals, Inc., dated January 18, 2017	S-1	333-216949	10.6	March 27, 2017
10.10#	Strategic Collaboration, Option and License Agreement by and among Registrant and Novartis Pharma AG, dated January 5, 2017	S-1	333-216949	10.7	March 27, 2017
10.11	Stock Purchase Agreement by and among Registrant, Ionis Pharmaceuticals, Inc. and Novartis Pharma AG, dated January 5, 2017	S-1	333-216949	10.8	March 27, 2017
10.12*†	Non-Employee Director Compensation Plan				

Exhibit	Description	Incorporated by Reference			
		Schedule / Form	File Number	Exhibit	File Date
10.13†	Offer Letter Agreement between Registrant and Paula Soteropoulos, dated November 17, 2014	S-1	333-216949	10.12	March 27, 2017
10.14†	Offer Letter Agreement between Registrant and Jeffrey M. Goldberg, dated January 5, 2015	S-1	333-216949	10.13	March 27, 2017
10.15†	Offer Letter Agreement between Registrant and Louis St. L. O'Dea, dated January 18, 2016	S-1	333-216949	10.14	March 27, 2017
10.16#	Letter Agreement regarding Development, Commercialization and License Agreement between Registrant and Ionis Pharmaceuticals, Inc., dated January 18, 2017	S-1	333-216949	10.15	March 27, 2017
21.1*	Subsidiaries of the Registrant				
23.1*	Consent of Independent Registered Public Accounting Firm				
24.1*	Power of Attorney (included in the signature page to this Report)				
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				
32.1**	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				
101	The following financial statements from the Akcea Therapeutics, Inc. Annual Report on Form 10-K for the year ended December 31, 2018, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive loss, (iv) consolidated statements of stockholders' equity, (v) consolidated statements of cash flows and (vi) notes to consolidated financial statements (detail tagged).				

* Filed herewith.
** Furnished herewith.
† Indicates management contract or compensatory plan.
# Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portion have been filed separately with the Securities and Exchange Commission

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 on the 1st day of March, 2019.

AKCEA THERAPEUTICS, INC.

By: /s/ PAULA SOTEROPOULOS
Paula Soteropoulos
Chief Executive Officer and Director
(Principal executive officer)

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Paula Soteropoulos and Michael MacLean, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

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.

Signatures	Title	Date
/s/ PAULA SOTEROPOULOS Paula Soteropoulos	Chief Executive Officer and Director (Principal executive officer)	March 1, 2019
/s/ MICHAEL MACLEAN Michael MacLean	Chief Financial Officer (Principal financial and accounting officer)	March 1, 2019
/s/ SARAH BOYCE Sarah Boyce	President and Director	March 1, 2019
/s/ CHRISTOPHER GABRIELI Christopher Gabrieli	Chairman of the Board	March 1, 2019
/s/ EDWARD M. FITZGERALD Edward M. Fitzgerald	Director	March 1, 2019
/s/ ELAINE HOCHBERG Elaine Hochberg	Director	March 1, 2019
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director	March 1, 2019
/s/ SANDFORD D. SMITH Sandford D. Smith	Director	March 1, 2019
/s/ RICHARD A. MOSCICKI Richard A. Moscicki	Director	March 1, 2019
/s/ DAMIEN MCDEVITT Damien McDevitt	Director	March 1, 2019

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Akcea Therapeutics, Inc.

Opinion on the Financial Statements
We have audited the accompanying consolidated balance sheets of Akcea Therapeutics, Inc. (the Company) as of December 31, 2018 and 2017, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2018, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

Adoption of ASU No. 2014-09
As discussed in Note 1 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2017 and 2018 due to the adoption of ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606).

Basis for Opinion
These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2016.

Boston, Massachusetts
March 1, 2019

AKCEA THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31, 2018	December 31, 2017 (as revised)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 86,454	$ 58,367
Short-term investments	166,155	201,763
Accounts receivable	4,597	5,413
Other current assets	10,029	1,302
Total current assets	267,235	266,845
Property, plant and equipment, net	5,696	77
Licenses, net	88,914	1,221
Deposits and other assets	3,416	661
Total assets	$ 365,261	$ 268,804
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 12,068	$ 2,381
Payable to Ionis Pharmaceuticals, Inc.	18,901	14,365
Accrued compensation	8,583	4,083
Accrued liabilities	14,787	7,570
Current portion of deferred revenue	25,354	58,192
Other current liabilities	968	1,875
Total current liabilities	80,661	88,466
Long-term portion of deferred rent	4,442	12
Long-term portion of deferred revenue	3,434	12,501
Total liabilities	88,537	100,979
Stockholders' equity:		
Common stock, $0.001 par value; 125,000,000 and 100,000,000 shares authorized, 89,345,978 and 66,541,629 shares issued and outstanding at December 31, 2018 and 2017, respectively.	89	67
Additional paid-in capital	799,001	464,430
Accumulated other comprehensive loss	(324)	(451)
Accumulated deficit	(522,042)	(296,221)
Total stockholders' equity	276,724	167,825
Total liabilities and stockholders' equity	$ 365,261	$ 268,804

See accompanying notes.

AKCEA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except for share and per share data)

	Years Ended December 31,		
	2018	2017 (as revised)	2016
Revenue:			
Commercial revenue:			
Product revenue	$ 2,237	$ —	$ —
Licensing revenue	12,000	—	—
Total commercial revenue	14,237	—	—
Research and development revenue under collaborative agreement	50,630	43,401	—
Total revenue	64,867	43,401	—
Expenses:			
Cost of sales - product	1,820	—	—
Cost of sales - intangible asset amortization	2,713	—	—
Cost of license	7,200	—	—
Research and development	130,340	126,890	68,459
Selling, general and administrative	153,610	36,981	15,053
Total expenses	295,683	163,871	83,512
Loss from operations	(230,816)	(120,470)	(83,512)
Other income (expense):			
Investment income	5,631	1,813	295
Interest expense	—	(1,731)	—
Other income (expense)	(189)	104	—
Loss before income tax expense	(225,374)	(120,284)	(83,217)
Income tax expense	(447)	(1,275)	—
Net loss	$ (225,821)	$ (121,559)	$ (83,217)
Net loss per share of preferred stock, basic and diluted	$ —	$ (1.80)	$ (2.88)
Weighted-average shares of preferred stock outstanding, basic and diluted	—	15,748,009	28,884,540
Net loss per share of common stock owned by Ionis, basic and diluted	$ (2.74)	$ (3.08)	$ —
Weighted-average shares of common stock outstanding owned by Ionis, basic and diluted	59,812,394	20,669,446	—
Net loss per share of common stock owned by others, basic and diluted	$ (2.87)	$ (3.08)	$ —
Weighted-average shares of common stock outstanding owned by others, basic and diluted	21,553,407	9,593,322	—

See accompanying notes.

AKCEA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Years Ended December 31,		
	2018	2017 (as revised)	2016
Net loss	$ (225,821)	$ (121,559)	$ (83,217)
Unrealized gains (losses) on investments, net of tax	144	(337)	75
Currency translation adjustment	(17)	(93)	(21)
Comprehensive loss	$ (225,694)	$ (121,989)	$ (83,163)

See accompanying notes.

AKCEA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
Years Ended December 31, 2018, 2017 and 2016
(In thousands)

Description	Convertible Preferred Stock Shares	Convertible Preferred Stock Amount	Common Stock Shares	Common Stock Amount	Additional Paid In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit (as revised)	Total Stockholders' Equity (Deficit) (as revised)
Balance at December 31, 2015	28,885	$ 100,000	—	$ —	$ 46,787	$ (75)	$ (91,445)	$ 55,267
Net loss	—	—	—	—	—	—	(83,217)	(83,217)
Change in unrealized gains, net of tax	—	—	—	—	—	75	—	75
Currency translation adjustment	—	—	—	—	—	(21)	—	(21)
Stock-based compensation expense	—	—	—	—	10,149	—	—	10,149
Balance at December 31, 2016	28,885	$ 100,000	—	$ —	$ 56,936	$ (21)	$ (174,662)	$ (17,747)
Net loss	—	—	—	—	—	—	(121,559)	(121,559)
Change in unrealized gains (losses), net of tax	—	—	—	—	—	(337)	—	(337)
Currency translation adjustment	—	—	—	—	—	(93)	—	(93)
Conversion of convertible preferred stock to common stock	(28,885)	(100,000)	28,885	29	99,971	—	—	—
Initial public offering of common stock, net of commissions, underwriting discounts and offering costs	—	—	17,969	18	132,273	—	—	132,291
Issuance of common stock in connection with conversion of line of credit with Ionis Pharmaceuticals Inc. together with accrued interest	—	—	13,438	14	107,717	—	—	107,731
Issuance of common stock in connection with private placement	—	—	6,250	6	49,994	—	—	50,000
Stock-based compensation expense	—	—	—	—	17,539	—	—	17,539
Balance at December 31, 2017	—	$ —	66,542	$ 67	$ 464,430	$ (451)	$ (296,221)	$ 167,825
Net loss	—	—	—	—	—	—	(225,821)	(225,821)
Change in unrealized gains (losses), net of tax	—	—	—	—	—	144	—	144
Currency translation adjustment	—	—	—	—	—	(17)	—	(17)
Exercise of common stock options	—	—	831	1	6,621	—	—	6,622
Issuance of common stock in connection with employee stock purchase plan	—	—	32	—	341	—	—	341
Issuance of restricted common stock	—	—	5	—	—	—	—	—
Stock compensation expense	—	—	—	—	44,282	—	—	44,282
Issuance of common stock to Ionis in connection with TTR License Agreement	—	—	18,667	18	200,094	—	—	200,112
Distribution to Ionis in connection with the TTR license transaction	—	—	—	—	(7,792)	—	—	(7,792)
Issuance of common stock to Ionis in connection with TEGSEDI regulatory milestones	—	—	3,269	3	89,997	—	—	90,000
Capital contribution from Ionis	—	—	—	—	1,028	—	—	1,028
Balance at December 31, 2018	—	—	89,346	$ 89	$ 799,001	$ (324)	$ (522,042)	$ 276,724

See accompanying notes.

AKCEA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31,		
	2018	2017 (as revised)	2016
Operating activities:			
Net loss	$ (225,821)	$ (121,559)	$ (83,217)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	307	108	12
Amortization of licenses	2,870	120	119
Amortization of discount/premium on investment securities, net	(23)	499	170
Non-cash interest expense for line of credit with Ionis Pharmaceuticals, Inc.	—	1,731	—
Non-cash sublicensing expense	—	33,394	—
Stock-based compensation expense	44,282	17,539	10,149
Changes in operating assets and liabilities:			
Accounts receivable	816	(5,413)	—
Other current and long-term assets	(8,765)	(1,761)	64
Accounts payable	8,444	1,905	(54)
Payable to Ionis Pharmaceuticals, Inc.	4,527	(43,385)	15,157
Accrued compensation	4,500	1,578	1,582
Deferred rent	1,203	(15)	20
Accrued liabilities	7,217	6,587	637
Income taxes payable	(540)	1,789	—
Deferred revenue	(41,905)	70,693	—
Net cash used in operating activities	(202,888)	(36,190)	(55,361)
Investing activities:			
Purchases of short-term investments	(136,895)	(301,377)	(16,638)
Proceeds from sale of short-term investments	208,559	98,778	51,464
Purchase of property, plant and equipment	(1,119)	(9)	(179)
Net cash provided by (used in) investing activities	70,545	(202,608)	34,647
Financing activities:			
Proceeds from exercise of common stock options and employee stock purchase plan issuances	6,963	—	—
Proceeds from issuance of common stock, net of underwriters' discount	—	135,438	—
Proceeds from sale of common stock to Novartis in private placement	—	50,000	—
Proceeds from line of credit from Ionis Pharmaceuticals, Inc.	—	106,000	—
Net proceeds from issuance of common stock to Ionis in connection with TTR License Agreement	155,868	—	—
Offering costs paid	—	(2,037)	(818)
Net cash provided by (used in) financing activities	162,831	289,401	(818)
Effect of exchange rates on cash	(17)	(93)	—
Net increase (decrease) in cash and cash equivalents	30,471	50,510	(21,532)
Cash, cash equivalents and restricted cash at beginning of period	58,367	7,857	29,389
Cash, cash equivalents and restricted cash at end of period	$ 88,838	$ 58,367	$ 7,857
Supplemental disclosures of non-cash investing and financing activities:			
Unpaid deferred offering costs	$ —	$ —	$ 291
Conversion of preferred stock to common stock upon initial public offering	$ —	$ 100,000	$ —
Conversion of line of credit from Ionis Pharmaceuticals, Inc. into common stock	$ —	$ 107,731	$ —
Purchase of property, plant and equipment included in accounts payable	$ 1,252	$ —	$ —
Purchase of property, plant and equipment included in long-term deferred rent liability	$ 3,555	$ —	$ —
Acquisition of research and development licenses and milestone payments	$ 90,563	$ —	$ —
Capital contribution from Ionis	$ 1,028	$ —	$ —

See accompanying notes.

	Years Ended December 31,		
	2018	2017	2016
Cash and cash equivalents	$ 86,454	$ 58,367	$ 7,857
Restricted cash included in deposits and other assets	2,384	—	—
Total cash, cash equivalents and restricted cash	$ 88,838	$ 58,367	$ 7,857

See accompanying notes.

1. Organization and Basis of Presentation

We were incorporated in Delaware in December 2014. We were organized by Ionis Pharmaceuticals, Inc., or Ionis, to focus on developing and commercializing drugs to treat patients with rare and serious diseases. On July 19, 2017, we completed our initial public offering, or IPO. As of December 31, 2018, Ionis owned approximately 75% of our common stock and is our majority shareholder. Prior to our IPO, we were wholly owned by Ionis.

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America, or U.S. GAAP. Certain amounts in the prior period financial statements have been revised to conform to the presentation of the current period financial statements. See Note 2, *Summary of Significant Accounting Policies*, for a discussion of these revisions to prior period financial statements made in connection with our adoption of the new revenue recognition guidance retroactive to January 1, 2016.

The consolidated financial statements include the accounts of Akcea Therapeutics, Inc. ("we," "our," and "us") and our wholly owned subsidiaries. All intercompany transactions and balances were eliminated in consolidation. We included all normal recurring adjustments in the financial statements, which we considered necessary for a fair presentation of our financial position and our operating results and cash flows for the years ended December 31, 2018, 2017 and 2016.

In accordance with Accounting Standard Codification, or ASC, 205-40, *Going Concern*, we evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date that the consolidated financial statements are issued. We have incurred losses since our inception and have funded our cash flow deficits primarily through the issuance of capital stock and the proceeds from licensing and collaboration agreements. As of December 31, 2018, we had an accumulated deficit of $522.0 million. During the year ended December 31, 2018, we incurred a loss of $225.8 million and used $202.9 million of cash in operations. We expect to continue to generate operating losses and negative operating cash flows for the foreseeable future. The transition to profitability is dependent upon the successful development, approval, and commercialization of our products and product candidates and the achievement of a level of revenue adequate to support our cost structure. We believe that our currently available funds of $252.6 million as of December 31, 2018, together with the receipt of the $150.0 million license fee payment expected in March 2019 as a result of Novartis opt in for the ACKEA-APO(a)-L_{Rx}, and cash expected to be generated from sales of TEGSEDI, which has been approved in the U.S., the EU and Canada, will be sufficient to fund our operations through at least the next 12 months from the issuance of this Annual Report on Form 10-K. Management's belief with respect to its ability to fund operations is based on estimates that are subject to risks and uncertainties. If actual results are different from management's estimates, we may need to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and commercialize our drugs even if we would otherwise prefer to develop and commercialize the drugs ourselves.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these financial statements include, but are not limited to, revenue recognition, the accrual for research and development expenses and prior to our IPO, the valuation of common stock. Estimates are periodically reviewed in light of changes in facts, circumstances and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from those estimates.

Translation of Foreign Currency

For our foreign subsidiaries that report in a functional currency other than U.S. dollars, we translate their assets and liabilities into U.S. dollars using the exchange rate at the balance sheet date. We translate revenue and expenses at the monthly average exchange rates for the period. We translate transactions in our capital accounts at the historic exchange rate in effect at the date of the transaction. We include foreign currency translation adjustments as a component of accumulated other comprehensive loss within the consolidated statements of comprehensive loss.

Concentration of Credit Risk

Financial instruments that potentially subject us to concentrations of credit risk consist primarily of cash, cash equivalents, short-term investments and accounts receivables. We place our cash, cash equivalents and short-term investments with reputable financial institutions. We primarily invest our excess cash in commercial paper and debt instruments of the U.S. Treasury, financial institutions, corporations and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, Standard & Poor's, or S&P, or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

Cash Equivalents and Short-Term Investments

We consider all liquid investments with maturities of three months or less when we purchase them to be cash equivalents. Our short-term investments have initial maturities of greater than three months from date of purchase. We classify our short-term investments as available-for-sale and we carry them at fair market value based upon prices for identical or similar items on the last day of the fiscal period. We record unrealized gains and losses as a separate component of comprehensive income (loss) and we include net realized gains and losses in investment income (expense) on our consolidated statement of operations. We use the specific identification method to determine the cost of securities sold.

Inventory

Prior to the regulatory approval of our product candidates, we incur expenses for the manufacturing of drug product that could potentially be available to support the commercial launch of our products. Until the first reporting period when regulatory approval has been received or is otherwise considered probable, we record all such costs as research and development expense.

For TEGSEDI inventory related costs incurred subsequent to July 1, 2018, we reflected these amounts as inventory on our consolidated balance sheets at the lower of cost or market value under the first-in, first-out, or FIFO, basis. We periodically analyze our inventory levels, and write down inventory that has become obsolete, inventory that has a cost basis in excess of its estimated realizable value and inventory in excess of expected sales requirements as cost of product sales. The determination of whether inventory costs will be realizable requires estimates by our management and if actual market conditions are less favorable than projected by our management, additional write-downs of inventory may be required which would be recorded as a cost of product sales in the consolidated statements of operations.

At December 31, 2018 a majority of our physical inventory for TEGSEDI was produced prior to when we obtained regulatory approval and accordingly had no cost basis as we recorded the related costs as research and development expense in prior periods. At December 31, 2018 the amount of finished goods recorded in our consolidated balance sheets in other current assets related to our approved product TEGSEDI was $85,000.

Property and Equipment

Property and equipment are recorded at cost and depreciated over their estimated useful lives using the straight-line method over the estimated useful life of each asset. Furniture and fixtures are depreciated over seven years. Leasehold improvements are amortized over the shorter of the lease term or the ten-year estimated useful life of the asset. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is credited or charged to income. Repairs and maintenance costs are expensed as incurred.

Intangible Assets

We obtained exclusive licenses from Ionis for specific patents that Ionis owns and maintains related to our drug pipeline. We recorded our licenses from Ionis as a capital contribution using the carryover basis of Ionis' historical cost for the related patents. We are amortizing our capitalized licenses over their estimated useful life, which is the term of the underlying individual patents owned by Ionis.

In addition, we maintain definite-lived intangible assets related to regulatory milestone payments made to Ionis that are recoverable through future cash flows from approved products, which are capitalized as license intangible assets. These assets are amortized over their remaining useful lives, which are generally estimated to be the remaining patent life. If our estimate of the product's useful life is shorter than the remaining patent life, then the shorter period is used. Intangible assets are amortized using the economic consumption method if anticipated future revenue can be reasonably estimated. The straight-line method is used when future revenue cannot be reasonably estimated. Amortization expense is recorded as a component of cost of sales to the extent the underlying license is commercialized or research and development prior to its commercialization in the consolidated statements of operations.

Fair Value of Financial Instruments

We have estimated the fair value of our financial instruments. The amounts reported for cash equivalents, accounts payable and accrued expenses approximate fair value because of their short maturities. We report our investment securities at their estimated fair value based on a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities; Level 2, defined as inputs other than quoted prices in active markets that are either directly or indirectly observable, which includes our fixed income securities and commercial paper classified as available-for-sale securities; and Level 3, defined as unobservable inputs in which little or no market data exists, therefore requiring us to develop our own assumptions. We have not historically held any Level 3 investments. Our securities have been classified as Level 1 or Level 2. We obtain the fair value of our Level 2 investments from our custodian bank and from a professional pricing service. We validate the fair value of our Level 2 investments by understanding the pricing model used by the custodian banks or professional pricing service provider and comparing that fair value to the fair value based on observable market prices. We recognize transfers between levels of the fair value hierarchy on the date of the event or change in circumstances that caused the transfer.

Revenue Recognition

Collaboration and License Revenue

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014-09, which amended the guidance for accounting for revenue from contracts with customers. This ASU superseded the revenue recognition requirements in ASC Topic 605, *Revenue Recognition*, or Topic 605, and created a new Topic 606, *Revenue from Contracts with Customers*, or Topic 606. Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services.

To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. At contract inception, once the contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations, then assess whether each promised good or service is distinct. When we offer options for additional goods or services, such as an option to license a drug in the future or for additional goods or services to be provided in the future, we evaluate whether such options are material rights that should be treated as additional performance obligations. We typically have not concluded that the option to license a drug or the options for additional goods or services that may be requested in the future under our collaboration agreement are material rights as the amounts attributable to such options represent standalone selling price, and therefore no consideration is allocated to these items at the inception of an agreement. When a partner exercises its option to license a drug or requests the additional goods or services, a new performance obligation is created for that item. Once performance obligations are identified, we then recognize as revenue the amount of the transaction price that we allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time. If the performance obligation is satisfied over time, we recognize revenue based on the use of an output or input method. As of December 31, 2018, we have three revenue streams: our strategic collaboration, option and license

agreement, or collaboration agreement, with Novartis Pharma AG, or Novartis, which we entered into in January 2017, our collaboration and license agreement with PTC Therapeutics International Limited, or PTC Therapeutics, which we entered into in August 2018 and commercial product revenue related TEGESDI sales subsequent to product launch in the fourth quarter of 2018. For a complete discussion of the accounting for our revenue streams, see Note 6, *Strategic Collaboration with Novartis*, Note 8, *Collaboration and License Agreement with PTC Therapeutics*, and Note 2, *Summary of Significant Accounting Policies*.

Effective January 1, 2018, we adopted Topic 606 using the full retrospective transition method. Under this method, we revised our consolidated financial statements for prior period amounts including the periods included in this Report on Form 10-K, as if Topic 606 had been effective for such periods. The references "as revised" used herein refer to revisions of amounts originally reported for the year ended December 31, 2017 and as of December 31, 2017 as a result of our adoption of Topic 606.

Impact of Adoption

As a result of adopting Topic 606 on January 1, 2018, we revised our comparative financial statements for the prior years as if Topic 606 had been effective for that period. On September 18, 2018, we filed a Current Report on Form 8-K to present recast consolidated financial statements for each of the three years ended December 31, 2015, 2016 and 2017, to reflect our adoption of the new accounting standard for revenue recognition set forth in Topic 606. The financial information recast in the Form 8-K was originally filed with the SEC in our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, which was filed with the SEC on February 28, 2018. Under Topic 605, we recognized revenue from our collaboration with Novartis over time on a straight-line basis. Under Topic 606, we recognize revenue from our collaboration with Novartis using the input method based on the total cost of performing services over time. As a result, the following financial statement line items for fiscal year 2017 were affected.

Consolidated Balance Sheets

	December 31, 2017 (in thousands)		
	As Revised Under Topic 606	As Originally Reported Under Topic 605	Effect of Change
Current portion of deferred revenue	$ 58,192	$ 50,579	$ 7,613
Long-term portion of deferred revenue	12,501	8,306	4,195
Accumulated deficit	$ (296,221)	$ (284,413)	$ (11,808)

Consolidated Statements of Operations and Comprehensive Loss

	Year Ended December 31, 2017 (in thousands, except per share data)		
	As Revised Under Topic 606	As Originally Reported Under Topic 605	Effect of Change
Research and development revenue under collaborative Agreement	$ 43,401	$ 55,209	$ (11,808)
Loss from operations	(120,470)	(108,662)	(11,808)
Net loss	(121,559)	(109,751)	(11,808)
Net loss per share of preferred stock, basic and diluted	(1.80)	(1.55)	(0.25)
Net loss per share of common stock owned by Ionis, basic and diluted	(3.08)	(2.82)	(0.26)
Net loss per share of common stock owned by others, basic and diluted	$ (3.08)	(2.82)	$ (0.26)

Consolidated Statement of Cash Flows

	Years Ended December 31, 2017 (in thousands)		
	As Revised Under Topic 606	As Originally Reported Under Topic 605	Effect of Change
Net loss	$ (121,559)	$ (109,751)	$ (11,808)
Adjustments to reconcile net loss to net cash used in operating activities:			
Deferred revenue	70,693	58,885	11,808
Cash, cash equivalents and restricted cash at beginning of period	7,857	7,857	—
Cash, cash equivalents and restricted at end of period	$ 58,367	$ 58,367	$ —

Product Revenue, Net

Subsequent to regulatory approval in Europe on July 11, 2018 and FDA approval in the U.S. on October 5, 2018, in the fourth quarter of 2018 we began to sell TEGSEDI in the U.S. and Germany. In the U.S., the product is distributed through an exclusive distribution agreement with a third-party logistics (3PL) company that takes title to the product and represents our sole customer in the U.S. Our U.S. customer distributes TEGSEDI to a specialty pharmacy and a specialty distributor (collectively referred to as "wholesalers"), who then distribute the product to health care providers and patients. In Germany, the product is distributed through a non-exclusive distribution model with a 3PL that takes title to the product and currently represents our sole customer in Germany. Our customer in Germany then distributes TEGSEDI to hospitals and pharmacies in Germany.

Revenue from product sales are recognized when the customer obtains control of our product, which occurs at a point in time, upon transfer of title to the customer. We record shipping and handling costs within cost of goods sold on our consolidated statement of operations. We classify payments to customers or other parties in the distribution channel for services that are distinct and priced at fair value as selling, general and administrative expenses in our consolidated statements of operations. Otherwise payments to customers or other parties in the distribution channel that do not meet those criteria are classified as a reduction of revenue, as discussed further below. Taxes collected from customers relating to product sales and remitted to governmental authorities are excluded from revenue. We have elected not to adjust consideration for the effects of a significant financing component when the period between the transfer of a promised good or service to the customer and when the customer pays for that good or service will be one year or less. Our payment terms are generally between thirty to ninety days. We expense incremental costs of obtaining a contract as and when incurred since the expected amortization period of the asset that we would have recognized is one year or less.

Reserves for Variable Consideration

Revenues from product sales are recorded at the net sales price (transaction price), which includes estimates of variable consideration for which reserves are established and which result from discounts, returns, chargebacks, rebates, co-pay assistance and other allowances that are offered within contracts between us and our customers, wholesalers, health care providers and other indirect customers relating to the sale of TEGSEDI. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (if the amount is payable to the customer) or a current liability (if the amount is payable to a party other than a customer). Where appropriate, these estimates take into consideration a range of possible outcomes that are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that it is considered probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

The following are the components of variable consideration related to product revenue:

Chargebacks: In the U.S., we estimate obligations resulting from contractual commitments with the government and other entities to sell products to qualified healthcare providers at prices lower than the list prices charged to our U.S. customer. Our U.S. customer charges us for the difference between what they pay for the product and the selling price to the qualified healthcare providers. We record reserves for these chargebacks related to product sold to our U.S. customer during the reporting period, as well as our estimate of product that remains in the distribution channel at the end of the reporting period that we expect will be sold to qualified healthcare providers in future periods.

Government rebates: We are subject to discount obligations under government programs, including Medicaid programs and Medicare in the United States. We estimate Medicaid and Medicare rebates based upon a range of possible outcomes that are probability-weighted for the estimated payer mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue and the establishment of a liability that is included in accrued expenses on our consolidated balance sheet. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program. On a quarterly basis, we update our estimates and record any adjustments in the period that we identify the adjustments. In Germany, pharmaceutical companies must grant a specified rebate percentage to the German government. We have included this rebate as a reduction of revenue in the period the related product revenue is recognized.

Trade discounts and allowances: We provide customary invoice discounts on TEGSEDI sales to our U.S. customer for prompt payment that are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, we receive and pay for various distribution services from our U.S. customer and wholesalers in the U.S. distribution channel. For services that are either not distinct from the sale of our product or for which we cannot reasonably estimate the fair value, such fees are classified as a reduction of product revenue.

Product Returns: Our U.S. customer has return rights and the wholesalers have limited return rights primarily related to the product's expiration date. We estimate the amount of product sales that may be returned and record the estimate as a reduction of revenue and a refund liability in the period the related product revenue is recognized. Based on the distribution model for TEGSEDI, contractual inventory limits with our customer and wholesalers and the price of TEGSEDI, we believe there will be minimal returns. Our customer in Germany only takes title to the product once it receives an order from a hospital or pharmacy and therefore does not maintain any inventory of TEGSEDI. Therefore, there is limited return risk and the Company has not recorded any return estimate in the transaction price for TEGSEDI sold in Germany.

Other incentives: In the U.S., other incentives include co-payment assistance we provide to patients with commercial insurance that have coverage and reside in states that allow co-payment assistance. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that we expect to receive associated with product that has been recognized as revenue. The estimate is recorded as a reduction of revenue in the same period the related revenue is recognized.

During the year ended December 31, 2018, we recorded product revenue, net, of $2.2 million, which consist of $1.2 million of TEGSEDI sales in the U.S., and $1.0 million of TEGSEDI sales in Germany. The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the year ended December 31, 2018 (in thousands):

	Chargebacks, discounts and fees	Government and other rebates	Returns	Total
Balance at December 31, 2017	$ —	$ —	$ —	$ —
Provision related to current period sales	50	293	5	348
Adjustment related to prior period sales	—	—	—	—
Credit or payments made during the period	—	—	—	—
Balance at December 31, 2018	$ 50	$ 293	$ 5	$ 348

Cost of Product Sales

As a result of receiving marketing authorization, or MA, approval for TEGSEDI from the European Commission, or EC, in July 2018, we began recording all TEGSEDI related expenses as cost of product sales starting in July 2018. Cost of product sales consists of manufacturing costs, transportation and freight, and indirect overhead costs associated with the manufacturing and distribution of TEGSEDI. Cost of product sales may also include period costs related to certain manufacturing services and inventory adjustment charges. Additionally, we expensed a significant portion of the cost of producing TEGSEDI that we will use in the commercial launch as research and development expense prior to the regulatory approval of TEGSEDI.

Commercial Sublicensing Expenses

We incur sublicense expenses under our TTR Development, Commercialization, Collaboration and License Agreement with Ionis related to the drugs we have licensed under the agreement. We include our sublicense fee expenses in our cost of license expenses on our consolidated statements of operations for those drugs that are approved for marketing. We recognize sublicense fee expenses in the period they are incurred.

Research and Development Expenses

Our research and development expenses include wages, benefits, facilities, supplies, external services, clinical study and manufacturing costs and other expenses that are directly related to our research and development activities. We expense research and development costs as we incur them. We do not conduct research activities and no such costs are included in these amounts.

If we make payments for research and development services prior to the services being rendered, we record those amounts as prepaid assets on our balance sheet and we expense them as the services are provided.

Research and Development Sublicensing Expenses

We incur sublicense expenses under our cardiometabolic development, commercialization and license agreement and services agreement with Ionis related to the drugs we have licensed under the agreement. We include our sublicense fee expenses in our research and development expenses on our consolidated statements of operations since the applicable drugs are not yet approved for marketing. We recognize sublicense fee expenses in the period they are incurred.

Estimated Liability for Research and Development Costs

We record accrued liabilities related to expenses for which vendors or service providers have not yet billed us. These liabilities are for products or services that we have received and primarily relate to ongoing nonclinical and clinical studies. These costs primarily include third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have drugs in concurrent nonclinical and clinical studies at several sites throughout the world. To ensure that we have adequately provided for ongoing nonclinical and clinical research and development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. Our historical accrual estimates have not been materially different from our actual amounts.

Stock-Based Compensation Expense

We measure stock-based compensation expense for equity-classified awards, principally related to stock options, restricted stock units, or RSUs, and stock purchase rights under our employee stock purchase plan, or ESPP, based on the estimated fair value of the award on the date of grant. We recognize the value of the portion of the award that we ultimately expect to vest as stock-based compensation expense over the requisite service period in our consolidated statements of operations. We reduce stock-based compensation expense for estimated forfeitures at the time of grant and revise the expense in subsequent periods if actual forfeitures differ from those estimates.

We value our stock option awards and stock purchase rights under our ESPP using the Black-Scholes model. The determination of the grant date fair value of options using an option pricing model is affected principally by our estimated common stock fair value and requires us to make a number of other assumptions, including: the expected life of the option, the volatility of the underlying stock, the risk-free interest rate and expected dividends.

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted vest annually over a four-year period.

Prior to December 2015, Ionis granted our employees options to purchase shares of Ionis' common stock, or Ionis options. In December 2015, we granted our employees holding Ionis options additional options to purchase shares of our common stock, or Akcea options.

We determined the stock-based compensation expense for the Ionis options at the date of grant and recognized compensation expense over the vesting period of the Ionis options. In December 2015, we accounted for the issuance of the Akcea options as a modification to the original grant of the Ionis options because the grant of the Ionis options and Akcea options essentially represented a single stock award as the exercisability provisions of the Ionis options and Akcea options grants were interrelated and mutually exclusive. The total compensation expense measured on the modification date was the sum of the grant date fair value of the Ionis options plus any incremental compensation cost resulting from the grant of the Akcea options.

In 2016, we began concurrently granting Ionis options and Akcea options to our employees. Because the exercisability provisions of the awards are interrelated and mutually exclusive as described above, the fair values of the Ionis options and the Akcea options were determined on the date of grant and the option with the greater fair value was recognized over the vesting period of the awards. In 2017, we no longer concurrently granted Ionis and Akcea options. Our board of directors only receive grants under the Akcea option plan.

Following our IPO, we no longer grant Ionis options to our employees. Under the terms of the Ionis options, when we completed our IPO, the Ionis options our employees were holding were terminated. The termination of the Ionis options was determined not to be a modification, as the options were terminated based upon the existing contractual terms of the option agreements. As such, we will continue to recognize expense based on the valuation that was determined upon the grant date for options issued in 2016 or the modification date for options issued in 2015 and 2017.

The fair value of stock options granted under our 2015 Equity Incentive Plan is based on the fair value of our common stock on the date of grant. The fair value of stock options granted under the Ionis 2011 Equity Incentive Plan is based on the fair value of Ionis' common stock on the date of grant. Options granted to employees vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of ten years. Options granted to directors vest annually over a four-year period and have a term of ten years.

See Note 9, *Equity and Stock-based Compensation*, for additional information regarding our stock-based compensation plans.

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is comprised of unrealized gains and losses on investments, net of taxes and currency translation adjustments. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Beginning balance accumulated other comprehensive loss	$ (451)	$ (21)	$ (75)
Unrealized gains (losses) on investments, net of tax (1)	144	(337)	75
Currency translation adjustment	(17)	(93)	(21)
Net other comprehensive income (loss)	127	(430)	54
Ending balance accumulated other comprehensive loss	$ (324)	$ (451)	$ (21)

(1) There was no tax benefit for other comprehensive income (loss) for the years ended December 31, 2018, 2017 and 2016.

Income Taxes

On December 22, 2017, the United States enacted H.R.1., known as the Tax Cuts and Jobs Act, which represented a substantial change to tax laws in the United States. The SEC staff subsequently issued Staff Accounting Bulletin No. 118, *Income Tax Accounting Implications of the Tax Cuts and Jobs Act* ("SAB 118"), which allowed us to record provisional amounts during a measurement period not to extend beyond one year of the enactment date. For the year ended December 31, 2017, we recorded provisional amounts in accordance SAB 118 where it was possible to make reasonable estimates of the effects of the Tax Act. All aspects of the Tax Act were accounted for prior to the closure of the one-year measurement period provided by SAB 118 and our accounting for these matters is now complete.

Prior to the completion of our IPO we filed our tax returns on a consolidated and combined basis with Ionis for federal and state income tax purposes, respectively. For financial statement purposes when we are required to file on a consolidated or combined basis, we calculate our income tax amounts, including net operating losses and tax credit carryforwards, using a separate return methodology which determines income taxes as if we were a separate taxpayer from Ionis. Effective July 19, 2017, the date of our IPO, we are no longer included in the consolidated federal income tax return with Ionis. We determined the amount of federal tax attributes, primarily net operating losses and tax credit carryforwards that transferred to us upon deconsolidation from Ionis. We are still required to file most of our state tax returns on a consolidated or combined basis with Ionis. Therefore, for financial statement purposes we calculated our state income tax amounts using the separate return method.

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in our financial statements or tax returns. In addition, deferred tax assets are recorded for the future benefit of utilizing net operating losses and research and development credit carry forwards. Valuation allowances are provided when necessary to reduce deferred tax assets to the amount expected to be realized.

We apply the authoritative accounting guidance prescribing a threshold and measurement attribute for the financial recognition and measurement of a tax position taken or expected to be taken in a tax return. We recognize liabilities for uncertain tax positions based on a two-step process. The first step is to evaluate the tax position for recognition by determining if the weight of available evidence indicates that it is more likely than not that the position will be sustained on audit, including resolution of related appeals or litigation settlement. The second step is to estimate and measure the tax benefit as the largest amount that is more than 50% likely to be realized upon ultimate settlement.

We recognize interest and penalties related to unrecognized tax benefits within the income tax expense line in the accompanying consolidated statements of operations. Accrued interest and penalties are included within other long-term liabilities in the consolidated balance sheets.

Significant judgment is required in evaluating our uncertain tax positions and determining our provision for income taxes. Although we believe our reserves are reasonable, no assurance can be given that the final tax outcome of these matters will not be different from that which is reflected in our historical income tax provisions and accruals. We adjust these reserves for changing facts and circumstances, such as the closing of a tax audit or the refinement of an estimate. To the extent that the final tax outcome of these matters is different than the amounts recorded, such differences may impact the provision for income taxes in the period in which such determination is made.

Significant judgment is also required in determining any valuation allowance recorded against deferred tax assets. In assessing the need for a valuation allowance, we consider all available evidence, including scheduled reversal of deferred tax liabilities, past operating results, the feasibility of tax planning strategies and estimates of future taxable income. Estimates of future taxable income are based on assumptions that are consistent with our plans. Assumptions represent management's best estimates and involve inherent uncertainties and the application of management's judgment. Should actual amounts differ from our estimates, the amount of our tax expense and liabilities could be materially impacted.

We record a valuation allowance to reduce the balance of our net deferred tax assets to the amount we believe is more-likely-than-not to be realized. We have incurred financial statement losses since inception and as a result we have a full valuation allowance recorded against our net deferred tax assets. We regularly assess the future realization of our net deferred tax assets and will reduce the valuation allowance in any such period in which we determine that all, or a portion, of our deferred tax assets are more-likely-than-not to be realized.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries. The earnings of non-U.S. subsidiaries are currently expected to be indefinitely reinvested in non-U.S. operations.

New Accounting Pronouncements - Recently Issued

In February 2016, the FASB issued amended accounting guidance related to lease accounting, which will require us to record all leases with a term longer than one year on our balance sheet. When we record leases on our balance sheet under the new guidance, we will record a liability with a value equal to the present value of payments we will make over the life of the lease (lease liability) and an asset representing the underlying leased asset (right of use asset). The new accounting guidance requires us to determine if our leases are operating or financing leases. We will record expense for operating leases on a straight-line basis as an operating expense. If we determine a lease is a financing lease, we will record both interest and amortization expense and generally the expense will be higher in the earlier periods of the lease. We adopted this guidance on January 1, 2019 and adjusted our opening balance sheet on that date. We elected the available practical expedients. The most significant impact was the recognition of right of use assets and lease liabilities for our operating leases. We are in the process of finalizing the impact of the adoption. The adoption will not have an impact in our consolidated statement of operations or statement of cash flows.

In February 2018, the FASB issued updated guidance for reclassification of tax effects from accumulated other comprehensive income (loss). The updated guidance gives entities an option to reclassify the stranded tax effects resulting from changes due to the Tax Act from accumulated other comprehensive income (loss) to retained earnings. The updated guidance is effective for all entities for fiscal years beginning after December 31, 2018, and interim periods within those fiscal years. Early adoption is permitted and adoption is optional. We are currently assessing the impact this updated guidance could have on our consolidated financial statements and the timing of potential adoption.

In June 2018, the FASB issued updated guidance to simplify the accounting for stock-based compensation expense for non-employees. We adopted this guidance in the second quarter of 2018. We have not granted stock options to non-employees as of December 31, 2018 and therefore this new guidance has no impact on our consolidated financial statements.

In August 2018, the FASB updated its disclosure requirements related to Level 1, 2 and 3 fair value measurements. The update included deletion and modification of certain disclosure requirements and additional disclosure related to Level 3 measurements. The guidance is effective for fiscal years beginning after December 15, 2019 and early adoption is permitted. We anticipate we will adopt this updated guidance on January 1, 2019 and we do not expect it to have a significant impact on our disclosures.

In August 2018, the FASB issued clarifying guidance on how to account for implementation costs related to hosted cloud-servicing arrangements. The primary change is to include any arrangement in which the customer accesses or uses software but does not take possession of the software when assessing for the capitalization of implementation costs of internal use software. Qualified costs are to be capitalized and amortized over the service period and they need to be expensed in the same line item as the service expense and recognized on the balance sheet in the same category as amounts prepaid for the hosted cloud-servicing arrangements generally as another asset. Cash flows related to the capitalized implementation costs should be presented consistent with the presentation of cash flows for the fees related to hosted cloud-servicing arrangements. The update can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. The updated guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted in any interim period. We are currently assessing the effects this updated guidance could have on our consolidated financial statements and timing of potential adoption.

In November 2018, the FASB issued clarifying guidance of the interaction between the collaboration accounting guidance and the new revenue recognition guidance we adopted on January 1, 2018 (Topic 606). The clarifying guidance included the following:

1) When a participant is considered a customer in a collaborative arrangement, all of the associated accounting under Topic 606 should be applied;
2) Adds “unit of account” concept to collaboration accounting guidance to align with Topic 606. This is used to determine if revenue is recognized or if a contra expense is recognized from consideration received under a collaboration; and
3) Precludes revenue from being recognized under Topic 606 when a transaction with a collaborative partner is determined not be a customer and is not directly related to the sales to third parties.

The updated guidance is effective for public entities for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years. Early adoption is permitted. We plan to adopt this guidance on January 1, 2020. We are currently assessing the effects it will have on our consolidated financial statements and disclosures.

3. Investments and Fair Value Measurements

Investments

As of December 31, 2018 and 2017, we primarily invested our excess cash in debt instruments of the U.S. Treasury, financial institutions, corporations and U.S. government agencies with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Moody's, S&P or Fitch, respectively. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. We periodically review and modify these guidelines to maximize trends in yields and interest rates without compromising safety and liquidity.

The following is a summary of our investments at December 31, 2018 and 2017 (in thousands):

December 31, 2018	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities	$ 81,770	$ —	$ (151)	$ 81,619
Debt securities issued by U.S. government agencies	85,578	—	(42)	85,536
Total securities with a maturity of one year or less	$ 167,348	$ —	$ (193)	$ 167,155

December 31, 2017	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities	$ 132,434	$ —	$ (206)	$ 132,228
Debt securities issued by U.S. government agencies	38,135	—	(59)	38,076
Total securities with a maturity of one year or less	170,569	—	(265)	170,304
Corporate debt securities	8,267	—	(35)	8,232
Debt securities issued by U.S. government agencies	23,264	—	(37)	23,227
Total securities with a maturity of one to two years	31,531	—	(72)	31,459
Total available-for-sale securities	$ 202,100	$ —	$ (337)	$ 201,763

We recorded unrealized losses related to the securities listed above as of December 31, 2018 and 2017. We believe that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate a full recovery of the amortized cost basis of our debt securities at maturity.

All of our available-for-sale securities are available to us for use in our current operations. As a result, we categorized all of these securities as current assets even though the stated maturity of some individual securities may be one year or more beyond the balance sheet date.

Fair Value Measurements

The following tables present the investments we held at December 31, 2018 and 2017 that are regularly measured and carried at fair value. The table segregates each security by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2018	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Money market funds (1)	$ 82,343	$ 82,343	$ —
Corporate debt securities (2)	81,619	—	81,619
Debt securities issued by U.S. government agencies (3)	85,536	—	85,536
Total	$ 249,498	$ 82,343	$ 167,155

	At December 31, 2017	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Money market funds (1)	$ 48,430	$ 48,430	$ —
Corporate debt securities (3)	140,460	—	140,460
Debt securities issued by U.S. government agencies (3)	61,303	—	61,303
Total	$ 250,193	$ 48,430	$ 201,763

(1) Included in cash and cash equivalents on our consolidated balance sheets.
(2) At December 31, 2018, $1.0 million was included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.
(3) Included in short-term investments on our consolidated balance sheets.

4. Property, Plant and Equipment

The following table presents property and equipment, at cost, and related accumulated depreciation (in thousands):

	December 31, 2018	2017
Furniture and fixtures	$ 1,611	$ 183
Computer equipment and software	102	15
Leasehold improvements	4,213	—
Total property and equipment, at cost	5,926	198
Less accumulated depreciation and amortization	(230)	(121)
Total property and equipment, net	$ 5,696	$ 77

Total depreciation expense amounted to $307,000, $108,000 and $12,000 for the years ended December 31, 2018, 2017 and 2016, respectively. As part of the operating lease for our new corporate headquarters, the landlord has provided a tenant improvement allowance of $3.6 million which is included in our leasehold improvements.

5. Intangible Assets

The following table presents intangible assets (in thousands):

	December 31, 2018	December 31, 2017	Estimated useful life
Acquired and in-licensed rights	$ 2,262	$ 1,699	7 - 21 Years
Capitalized regulatory approval milestones	90,000	—	16 Years
Less accumulated amortization	(3,348)	(478)	
Total intangible assets, net	$ 88,914	$ 1,221	

The increase in capitalized regulatory milestones as of December 31, 2018 was due to a milestone of $40.0 million paid to Ionis which was incurred upon the EU approval of TEDSEDI on July 11, 2018 and a milestone of $50.0 million paid to Ionis which was incurred upon the FDA approval of TEDSEDI on October 5, 2018.

The Company recorded $2.9 million, $0.1 million and $0.1 million, respectively, in amortization expense related to intangible assets during the years ended December 31, 2018, 2017 and 2016. Estimated future amortization expense for intangible assets as of December 31, 2018 is as follows (in thousands):

	Total
2019	$ 5,863
2020	5,879
2021	5,861
2022	5,856
2023	5,843
Thereafter	59,613
	$ 88,914

The weighted average remaining amortizable life of our patents was 12.15 years at December 31, 2018.

For additional detail of Akcea's license agreements with Ionis see Note 7, *License Agreements and Services Agreement with Ionis*.

6. Strategic Collaboration with Novartis

In January 2017, we initiated a strategic collaboration with Novartis for the development and commercialization of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Under the Novartis collaboration, Novartis has an exclusive option to further develop and commercialize these drugs. We are responsible for completing a Phase 2 program, conducting an end-of-Phase 2 meeting with the United States Food and Drug Administration, or FDA, and providing initial quantities of the active pharmaceutical ingredient, or API, for each drug. On September 24, 2018 Akcea and Ionis announced positive top-line results from the Phase 2 study of AKCEA-APO(a)-L_{Rx}. If Novartis exercises an option for one of these drugs, Novartis will be responsible for all further global development, regulatory and co-commercialization activities and costs for such drug.

We received a $75.0 million upfront payment in the first quarter of 2017, of which we retained $60.0 million and we paid Ionis $15.0 million as a sublicense fee under our Cardiometabolic License Agreement with Ionis. If Novartis exercises its option for a drug, Novartis will pay us a license fee equal to $150.0 million for each drug licensed by Novartis. In addition, for we are eligible to receive up to $675.0 million in milestone payments, including $25.0 million for the achievement of a development milestone, up to $290.0 million for the achievement of regulatory milestones and up to $360.0 million for the achievement of commercialization milestones. In addition, for AKCEA-APOCIII-L_{Rx}, we are eligible to receive up to $530.0 million in milestone payments, including $25.0 million for the achievement of a development milestone, up to $240.0 million for the achievement of regulatory milestones and up to $265.0 million for the achievement of commercialization milestones. We will earn the next milestone payment of $25.0 million under this collaboration if Novartis advances the Phase 3 study for either drug. We are also eligible to receive tiered royalties in the mid-teens to low twenty percent range on net sales of AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}. Novartis will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the product in a specific country. We will pay 50% of these license fees, milestone payments and royalties to Ionis as a sublicense fee. We may co-commercialize through our specialized sales force any licensed drug commercialized by Novartis in selected markets, under terms and conditions that we plan to negotiate with Novartis in the future.

At commencement of our strategic collaboration, we identified the following four distinct performance obligations:

- Development activities for AKCEA-APO(a)-L_{Rx};
- Development activities for AKCEA-APOCIII-L_{Rx};
- API for AKCEA-APO(a)-L_{Rx}; and
- API for AKCEA-APOCIII-L_{Rx}.

The development activities and the supply of API are distinct because Novartis or another third party could provide these items without our assistance.

We determined the transaction price for the Novartis collaboration was $108.4 million, comprised of the following:

- $75.0 million from the upfront payment we received;
- $28.4 million for the premium paid by Novartis, which represents the excess of the fair value Ionis received from Novartis' purchase of Ionis' stock at a premium in the first quarter of 2017; and
- $5.0 million for the premium Novartis would have paid to purchase Ionis' stock if we did not complete our IPO within 15 months of the inception of the agreement.

We are recognizing the $75.0 million upfront payment plus the premium paid by Novartis from its purchase of Ionis' stock and the premium associated with Novartis' obligation to purchase Ionis' stock if we did not complete our IPO because we are the party providing the services and API under the collaboration agreement.

None of the options or development or regulatory milestone payments under this agreement have been included in the transaction price as all payments are fully constrained. As part of our evaluation of the constraint, we considered numerous factors, including the fact that achievement of the milestones is outside of our control and contingent upon the success of our clinical trials, Novartis' efforts, and the receipt of regulatory approval. We will re-evaluate the transaction price, including estimated variable consideration included in the transaction price and all constrained amounts, in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

Based on the distinct performance obligations under the Novartis collaboration, we allocated the $108.4 million transaction price based on relative stand-alone selling prices of each of our performance obligations as follows:

- $64.0 million for development services for AKCEA-APO(a)-L_{Rx};
- $40.1 million for development services for AKCEA-APOCIII-L_{Rx};
- $1.5 million for the delivery of AKCEA-APO(a)-L_{Rx} API; and
- $2.8 million for the delivery of AKCEA-APOCIII-L_{Rx} API.

We are recognizing revenue related to each of our performance obligations as follows:

- We will satisfy the development services performance obligation for AKCEA-APO(a)-L_{Rx} as the research and development services are performed. A significant portion of the research and development services were completed by December 2018 with the remainder to be completed through mid-2019. We recognize revenue related to research and development services performed using an input method by calculating costs incurred at each period end relative to total costs expected to be incurred;

- We will satisfy the development services performance obligation for AKCEA-APOCIII-L_{Rx} as the research and development services are performed. We expect a significant portion of the research and development services to be completed by the end of December 2019 with the remainder through mid-2020. We recognize revenue related to research and development services performed using an input method by calculating costs incurred at each period end relative to total costs expected to be incurred;
- We recognized the amount attributed to the AKCEA-APO(a)-L_{Rx} API supply when we delivered API to Novartis in 2017; and
- We recognized the amount attributed to the AKCEA-APOCIII-L_{Rx} API supply when we delivered API to Novartis in May 2018.

Additionally, we and Ionis entered into a stock purchase agreement, or SPA, with Novartis. Under the SPA, in July 2017, Novartis purchased $50.0 million of our common stock in a separate private placement concurrent with the completion of our IPO at a price per share equal to the IPO price. Our IPO is discussed in Note 11, *Initial Public Offering*.

During the years ended December 31, 2018 and 2017 (as revised), we earned revenue of $50.6 million and $43.4 million, respectively, from our strategic collaboration with Novartis, representing 100% of our research and development revenue. We did not earn research and development revenue during the year ended December 31, 2016. During the year ended December 31, 2018 we recognized $42.2 million of revenue from amounts that were in our beginning deferred revenue balance. Our consolidated balance sheet at December 31, 2018 and 2017 (as revised) included deferred revenue of $28.8 million and $70.7 million, respectively, related to our strategic collaboration with Novartis.

7. License Agreements and Services Agreement with Ionis

In December 2015, we entered into a development, commercialization and license agreement related to our cardiometabolic franchise and a services agreement with Ionis. In March 2018, we entered into a new development, commercialization, collaboration and license agreement related to our TTR franchise and amended the services agreement previously in place with Ionis. The following sections summarize these related party agreements with Ionis.

Cardiometabolic Development, Commercialization and License Agreement

Our development, commercialization and license agreement, or Cardiometabolic License Agreement, with Ionis granted exclusive rights to us to develop and commercialize WAYLIVRA, AKCEA-APO(a)-L_{Rx}, AKCEA-APOCIII-L_{Rx}, and AKCEA-ANGPTL3-L_{Rx}, which are collectively referred to as the Lipid Drugs. Ionis granted us an exclusive license to certain patents to develop and commercialize products containing the Lipid Drugs. Ionis also granted us a non-exclusive license to the Ionis antisense platform technology for us to develop and commercialize products containing the Lipid Drugs. Ionis also granted us non-exclusive rights under its manufacturing technology to manufacture the Lipid Drugs in our own facility or at a contract manufacturer. As a part of this agreement both companies agreed not to work with any other parties to develop or commercialize other RNA-targeting drugs that are designed to inhibit any of the Lipid Drug targets so long as we are developing or commercializing the Lipid Drugs.

We and Ionis share development responsibilities for the Lipid Drugs. We pay Ionis for the research and development expenses it incurs on our behalf, which include both external and internal expenses. External research and development expenses include costs for contract research organizations, or CROs, costs to conduct nonclinical and clinical studies on our drugs, costs to acquire and evaluate clinical study data, such as investigator grants, patient screening fees and laboratory work, and fees paid to consultants. Internal research and development expenses include costs for the work that Ionis' research and development employees perform for us. Ionis charges us a full-time equivalent rate that covers personnel-related expenses, including salaries and benefits, plus an allocation of facility-related expenses, including rent, utilities, insurance and property taxes, for those development employees who work either directly or indirectly on the development of our drugs. We also pay Ionis for the API and drug product we use in our nonclinical and clinical studies for all of our drugs. Ionis manufactures the API for us and charges us a price per gram consistent with the price Ionis charges its pharmaceutical partners, which includes the cost for direct materials, direct labor and overhead required to manufacture the API. If we need the API filled in vials for our clinical studies and Ionis contracts with a third party to perform this work, Ionis will charge us for the resulting cost.

As we commercialize each of the Lipid Drugs, we will pay Ionis royalties from the mid-teens to the mid-twenty percent range on sales related to the Lipid Drugs that we sell. If we sell a Lipid Drug for a Rare Disease Indication (defined in the agreement as less than 500,000 patients worldwide or an indication that required a Phase 3 program of less than 1,000 patients and less than two years of treatment), we will pay a higher royalty rate to Ionis than if we sell a Lipid Drug for a Broad Disease Patient Population (defined in the agreement as more than 500,000 patients worldwide or an indication that required a Phase 3 program of 1,000 or more patients and two or more years of treatment). Other than with respect to the drugs licensed to Novartis under the collaboration agreement, if our annual sales reach $500.0 million, $1.0 billion and $2.0 billion, we will be obligated to pay Ionis sales milestones in the amount of $50.0 million for each sales milestone reached by each Lipid Drug. If and when triggered, we will pay Ionis each of these sales milestones over the subsequent 12 quarters in equal payments.

We may terminate this agreement if Ionis is in material breach of the agreement. Ionis may terminate this agreement if we are in material breach of the agreement. In each circumstance the party that is in breach will have an opportunity to cure the breach prior to the other party terminating this agreement.

In the first quarter of 2017, we entered into letter agreements with Ionis to reflect the agreed upon payment terms with respect to the upfront option payment that we received from Novartis and to allocate the premium that Novartis paid for Ionis' common stock in connection with our strategic collaboration with Novartis. For additional detail regarding our strategic collaboration with Novartis, see Note 6, *Strategic Collaboration with Novartis.*

TTR Development, Commercialization, Collaboration and License Agreement

On April 17, 2018, our stockholders, other than Ionis and its affiliates, approved the development, commercialization, collaboration and license agreement, or TTR License Agreement, and a stock purchase agreement, or Ionis SPA, with Ionis, our majority shareholder which was entered into on March 14, 2018. In addition, in connection with these agreements, we entered into an amended and restated services agreement, or Amended Services Agreement, and an amended and restated investor rights agreement, or Amended Investor Rights Agreement, with Ionis.

We determined that the TTR License Agreement and Ionis SPA included provisions which required the approval of the agreements by our stockholders other than Ionis and its affiliates, which we deemed was not perfunctory in nature, therefore, we concluded that the approved date of the agreements for accounting purposes was April 17, 2018, the date on which such approval was received and the closing of the agreements took place.

In accordance with the terms and provisions of the TTR License Agreement, we received rights to:

- commercialize TEGSEDI following receipt of regulatory approval and perform certain other non-commercial activities with respect to TEGSEDI, in each case, in accordance with a global strategic plan;
- partner on the completion of all pivotal studies, of a follow-on drug to TEGSEDI, AKCEA-TTR-L_{Rx} and perform other non-commercial activities with respect to AKCEA-TTR-L_{Rx};
- commercialize AKCEA-TTR-L_{Rx} following receipt of regulatory approval in accordance with a global strategic plan;
- share in profits and losses with respect to TEGSEDI and AKCEA-TTR-L_{Rx};
- manufacture (including through a third party) each product following receipt of regulatory approval for such product; and
- sublicense the development and commercialization of either product to third parties or affiliates, with the consent of Ionis.

As consideration for the grant of rights under the TTR License Agreement, we paid an upfront licensing fee of $150.0 million, which was paid through the issuance of 8 million shares of our common stock priced by reference to a trading average at the time of execution of the agreements. In addition, we are obligated to make milestone payments to Ionis in connection with the achievement of certain development, regulatory and commercialization events. These milestone payments include up to $110.0 million, if all TEGSEDI regulatory approval milestones are met; up to $145.0 million, if all AKCEA-TTR-L_{Rx} regulatory milestones are met; and a total of $1.3 billion, in the form of seven milestone payments, if all sales milestones for the combined products are met. We can elect to pay each milestone payment in cash or shares of our common stock and Ionis may require payment in shares of common stock up until the achievement of the milestone event for aggregate worldwide annual net sales of $750.0 million for the products. Subsequent to the achievement of the milestone event for aggregate worldwide annual net sales of $750.0 million, all subsequent milestone payments must be paid in cash.

Under the TTR License Agreement, we and Ionis also agreed to share TEGSEDI and AKCEA-TTR-L_{Rx} profits and losses as follows: for TEGSEDI, beginning on the earlier of (i) the first day of the quarter after receipt of regulatory approval of TEGSEDI in the United States, or (ii) January 1, 2019, the parties will share profits and losses from the development and commercialization of TEGSEDI (A) on a 60/40 basis (60% to Ionis and 40% to us) through the end of the quarter in which the first commercial sale of AKCEA-TTR-L_{Rx} occurs, and (B) on a 50/50 basis commencing on the first day of the first quarter thereafter; and for AKCEA-TTR-L_{Rx}, beginning January 1, 2018, the parties will share all profits and losses from the development and commercialization of AKCEA-TTR-L_{Rx} on a 50/50 basis.

The TTR License Agreement will remain in effect until the expiration of all included payment obligations, or unless earlier terminated. The TTR License Agreement can be terminated by mutual consent of us and Ionis, by either us or Ionis upon certain events, by either party upon material breach, or by Akcea for convenience upon providing 90 days written notice to Ionis. Upon termination all rights received under the TTR License Agreement will terminate.

To support the commercialization of TEGSEDI and AKCEA-TTR-L_{Rx}, Ionis purchased 10.7 million shares of our common stock for $200 million.

In connection with the licensing transaction, we amended our Certificate of Incorporation to increase our authorized shares of common stock from 100,000,000 shares to 125,000,000 shares.

We determined that the upfront accounting for the TTR License Agreement should follow the accounting guidance for common control transactions given the nature of the relationship between us and Ionis, including the fact that Ionis maintains a controlling ownership position in us.

In addition, we assessed the identifiable assets that were acquired under the terms of the TTR License Agreement, including the licensed rights to TEGSEDI and AKCEA-TTR-L_{Rx}, certain batches of TEGSEDI materials, the transfer of a minimal number of employees from Ionis to us and certain manufacturing and clinical research agreements. We concluded that the licensed rights represented a group of similar identifiable assets and that substantially all of the fair value of the acquisition resides in the licensed rights. As such, we concluded that the acquired assets did not meet the definition of a business and that we should account for the TTR License Agreement as an asset acquisition under common control guidance. Accordingly, we recorded the carrying value of the licensed rights held by Ionis of $0.6 million as an intangible asset at the date of acquisition and will amortize the amount over the remaining patent life.

In connection with the transaction, we also purchased $4.7 million of commercial TEGSEDI inventory held by Ionis. Prospectively we will be responsible for the procurement of all additional inventory. The inventory did not have a carrying value on the books of Ionis at the time of the acquisition. As such, in accordance with the accounting guidance for common control transactions above, we recorded the purchase of this inventory as a reduction of additional paid in capital. This amount represented a cash distribution to Ionis, therefore, we have included this distribution as a distribution to Ionis for purposes of loss per share and we have applied the two–class method as discussed in Note 13, *Basic and Diluted Net Loss Per Share*.

We also determined that the TTR License Agreement represented a collaboration arrangement as defined by ASC 808. Prior to April 1, 2018, Ionis was responsible for all costs associated with TEGSEDI and for the period from April 1, 2018 to December 31, 2018, we are responsible for all costs associated with TEGSEDI. We and Ionis share all costs associated with AKCEA-TTR-L_{Rx} from January 1, 2018 forward on a 50/50 basis. We recorded $3.1 million paid to Ionis for costs related to the period prior to the closing of the TTR license agreement to equity, as these amounts were previously expensed in the financial statements of Ionis. This amount also represents a cash distribution to Ionis and was included as an adjustment to the net loss attributable to Ionis for purposes of applying the two-class method for loss per share as discussed in Note 13, *Basic and Diluted Net Loss Per Share*. Any amounts paid to or received from Ionis subsequent to the closing of the TTR License Agreement will be recorded to expense based on the underlying nature of the activities.

During the year ended December 31, 2018, we recorded $26.0 million, as a component of research and development expense related to the TTR License Agreement. We did not record any research and development expense related to the TTR License Agreement in the years ended December 31, 2017 and 2016.

In addition, on July 11, 2018, we received marketing authorization, or MA, approval for TEGSEDI from the European Commission, or EC, for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis, or hATTR amyloidosis, in the European Union, or EU. As a result of the MA approval in the EU, on August 3, 2018, we issued 1,597,571 shares of our common stock to Ionis as payment of the $40.0 million regulatory approval milestone for TEGSEDI. As a result of the marketing authorization in the EU, we capitalized this regulatory approval milestone payment as a license intangible asset on our consolidated balance sheets as the amount in expected to be recoverable through future cash flows.

In addition, on October 5, 2018, we received regulatory approval for TEGSEDI from the FDA for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults in the United States. As a result of the regulatory approval in the United States, on October 17, 2018 we issued 1,671,849 shares of our common stock to Ionis as payment of the $50.0 million regulatory approval milestone for TEGSEDI. As a result of the FDA approval in the U.S., we capitalized this regulatory approval milestone payment as a license intangible asset on our consolidated balance sheets as the amount in expected to be recoverable through future cash flows.

Both milestone payments are being amortized to cost of sales on a straight-line basis over the licensed assets expected useful life of approximately 16 years from the date of the initial regulatory approval milestone achievement. Amortization expense for the TTR milestone payments was $2.7 million for the year ended December 31, 2018. We did not record any amortization expense for the TTR milestone payments for the years ended December 31, 2017 and 2016.

Services Agreement

We originally entered into a services agreement with Ionis in December 2015 in conjunction with the Cardiometabolic License Agreement. We entered into the Amended Services Agreement with Ionis in April 2018 in conjunction with the TTR License Agreement (collectively, the service agreements). The primary purpose of the Amended Services Agreement was to allow for the expansion of general and administrative services provided to us by Ionis to cover the TEGSEDI and AKCEA-TTR-L_{Rx} products under terms substantially similar to the prior services agreement.

Our services agreement with Ionis is designed to be flexible to adjust for our increasing capabilities in various functions. Under the services agreement, Ionis provides us certain services, including, without limitation, general and administrative support services and development support services. Ionis allocated a certain percentage of personnel to perform the services that it provides to us based on its good faith estimate of the required services. We pay Ionis for these allocated costs, which reflect the Ionis full-time equivalent, or FTE, rate for the applicable personnel, plus out-of-pocket expenses, such as occupancy costs, associated with the FTEs allocated to providing us these services. We do not pay a mark-up or profit on the external or internal expenses Ionis bills to us. Ionis invoices us quarterly for all amounts due under the services agreement and payments are due within 30 days of the receipt of an invoice.

In addition, as long as Ionis continues to consolidate our financials, we will comply with Ionis' policies and procedures and internal controls. As long as we are consolidated into Ionis' financial statements under U.S. GAAP, we may continue to access the following services from Ionis:

- investor relations services,
- human resources and personnel services,
- risk management and insurance services,
- tax related services,
- corporate record keeping services,
- financial and accounting services,
- credit services, and
- COO/CFO/CBO oversight.

However, if we wanted to provide the foregoing services internally, and doing so would not negatively impact Ionis' internal controls and procedures for financial reporting, we can negotiate in good faith with Ionis for a reduced scope of services related to the aforementioned services. When Ionis determines it should no longer consolidate our financials, we may mutually agree with Ionis in writing to extend the term of this arrangement in six-month increments.

We can establish our own benefits programs or continue to use Ionis' benefits, however we must provide Ionis a minimum advance notice to opt-out of using Ionis' benefits. We do not currently plan to establish our own benefits programs at this time or in the near future.

As of December 31, 2018 and 2017, we owed Ionis $18.9 million and $14.4 million, respectively.

The following table summarizes the amounts recorded related to transactions with Ionis including amounts related to the TTR licensing transaction for the following periods (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Operating expenses:			
Services performed by Ionis	$ 15,404	$ 9,742	$ 8,599
Active pharmaceutical ingredient manufactured by Ionis	5,229	6,012	12,648
Commercial inventory manufactured by Ionis	1,288	—	—
Sublicensing expenses	7,200	48,394	—
Out-of-pocket expenses paid by Ionis	50,870	37,426	42,367
Total operating expenses generated by transactions with Ionis	79,991	101,574	63,614
Distributions to Ionis:			
Commercial inventory manufactured by Ionis	4,707	—	—
Distribution to Ionis in connection with the TTR license transaction	3,085	—	—
Total distribution to Ionis	7,792	—	—
Total charges generated by transactions with Ionis	87,783	101,574	63,614
Payable balance to Ionis at the beginning of the period	14,365	24,355	9,198
Less: total amounts paid to Ionis during the period	(83,247)	(78,170)	(48,457)
Less: non-cash sublicensing expenses	—	(33,394)	—
Total amount payable to Ionis at period end	$ 18,901	$ 14,365	$ 24,355

8. Collaboration and License Agreement with PTC Therapeutics

In August 2018, we entered into a collaboration and license agreement with PTC Therapeutics, or the PTC License Agreement, to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries, or the PTC Territory.

We received a $12.0 million upfront payment from PTC Therapeutics related to TEGSEDI in the third quarter of 2018 upon execution of the PTC License Agreement, of which we paid Ionis $7.2 million as a sub-license royalty related to the TTR License Agreement. If WAYLIVRA is approved by the FDA or EMA, PTC Therapeutics will pay us $6.0 million. In addition, we are eligible to receive up to $8.0 million for the achievement of regulatory milestones and royalties in the mid-twenty percent range on net sales of TEGSEDI and WAYLIVRA in the PTC Territory. PTC Therapeutics' obligation to pay royalties to us begins on the earlier of 12 months after the first commercial sale of a product in Brazil or the date that PTC Therapeutics recognized revenue of at least $10.0 million in the PTC Territory. PTC Therapeutics will reduce these royalties upon the expiration of certain patents or if a generic competitor negatively impacts the market share of the product in the PTC Territory. Milestone payments and royalties that we are eligible to receive from PTC Therapeutics for TEGSEDI will be split 60% to Ionis and 40% to Akcea. All WAYLIVRA milestone payments and royalties that we are eligible to receive from PTC will be split 50/50 with Ionis. PTC Therapeutics is solely responsible for the commercialization of the products in the PTC Territory at its sole cost and expense, including the pursuit and maintenance of applicable regulatory approvals. Unless earlier terminated, the PTC License Agreement will continue in effect until the date on which the royalty term and all payment obligations with respect to all products in all countries in the PTC Territory have expired.

At the commencement of the PTC License Agreement, we identified two performance obligations, consisting of the transfer of (1) the license to TEGSEDI and related know-how and (2) the license to WAYLIVRA and related know-how, both of which were satisfied during the third quarter of 2018. In addition, we identified a customer option related to PTC Therapeutics option to purchase supply of product from us for its development and commercial needs. The option to purchase supply from us is subject to a supply agreement we are negotiating with PTC. We considered the manufacturing capabilities of PTC Therapeutics and the fact that manufacturing services are not proprietary and can be provided by other vendors, to conclude that the licenses have stand-alone functionality and are distinct. Further, the customer options for manufacturing of product is expected to be priced similar to other manufacturing options with similar customers and is therefore not considered a material right. As there were no remaining unsatisfied performance obligations as of September 30, 2018, the $12.0 million upfront payment was recognized as license revenue upon contract execution in the third quarter of 2018. None of the regulatory milestones have been included in the transaction price, as all

milestones were fully constrained. As part of our evaluation of the constraint, we considered numerous factors, including that regulatory approvals are not within our control and accordingly the related milestones are fully constrained and excluded from the arrangement consideration until such regulatory approvals are received. Any consideration related to sales-based royalties will be recognized when the related sales occur.

9. Equity and Stock-Based Compensation

Series A Convertible Preferred Stock

In December 2015, we issued and sold to Ionis an aggregate of 28,884,540 shares of Series A convertible preferred stock for a total purchase price of $100.0 million plus the grant of the rights and licenses we received under the development, commercialization and license agreement with Ionis. The $100.0 million of proceeds we received was recorded in Series A convertible preferred stock on our consolidated balance sheet. We had 28,884,540 shares of Series A convertible preferred stock authorized, issued and outstanding as of December 31, 2016, of which all was held by Ionis.

Conversion

Shares of our Series A convertible preferred stock were convertible 1:1 into common stock, subject to certain adjustments for reorganizations, reclassifications, stock splits, stock dividends and dilutive issuances. All shares of Series A convertible preferred stock automatically converted into common stock upon completion of the IPO in July 2017. As of December 31, 2018 and 2017, we had no shares of Series A convertible preferred stock issued or outstanding. Our IPO is discussed in Note 11, *Initial Public Offering*.

Preferred Stock

In July 2017, our board of directors approved an amendment and restatement of our certificate of incorporation to, among other things, change the authorized shares of our preferred stock to 10,000,000 shares with a par value of $0.001, all of which are undesignated. Our board of directors may establish the rights, preference and privileges of the preferred stock from time to time. The amended and restated certificate of incorporation was approved by our stockholders and became effective upon the completion of our IPO and the filing of the amended and restated certificate of incorporation with the State of Delaware in July 2017. As of December 31, 2018 and 2017, there were no shares of Preferred Stock outstanding.

Common Stock

At December 31, 2018 and 2017, we had 125,000,000 and 100,000,000, respectively shares of common stock authorized, of which 89,345,978 and 66,541,629 were issued and outstanding as of December 31, 2018 and 2017, respectively.

In May 2017, our board of directors approved an amendment to our certificate of incorporation to (1) effect a reverse stock split on outstanding shares of our common stock and preferred stock on a one-for-2.555 basis, (2) change the authorized shares of our preferred stock to 40,000,000 and (3) modify the threshold for automatic conversion of our preferred stock into shares of our common stock in connection with an IPO to eliminate the price per share threshold and only require that we raise at least $50.0 million in gross proceeds (collectively, the "Charter Amendment"). The par values of the common stock and preferred stock were not adjusted as a result of the reverse stock split. The amendment to our certificate of incorporation was approved by our stockholder and became effective upon the filing with the State of Delaware in June 2017. All issued and outstanding common stock and preferred stock and related share and per share amounts contained in these consolidated financial statements have been retroactively adjusted to reflect the reverse stock split for all periods presented.

Stock Plans

2015 Equity Incentive Plan

In December 2015, our board of directors and stockholder adopted and approved our 2015 Equity Incentive Plan, or the 2015 Plan. In May 2017 and June 2017, our board of directors and stockholder, respectively, approved an amendment to our 2015 Equity Incentive Plan in order to, among other things, increase the number of shares of common stock reserved for issuance thereunder to 8,500,000 shares of common stock in conjunction with the IPO.

As of December 31, 2018, the aggregate number of shares of common stock that may be issued pursuant to stock awards under the 2015 Plan was 18,500,000 shares. The 2015 Plan also provides for the grant of nonstatutory stock options, or NSOs, incentive stock options, or ISOs, stock appreciation rights, restricted stock awards and restricted stock unit awards. At December 31, 2018, a total of 11,010,828 options were outstanding, of which 4,305,172 were exercisable, 38,134 restricted stock unit awards were outstanding, and 1,610,490 shares were available for future grant under the 2015 Plan.

2017 Employee Stock Purchase Plan

In May 2017 and June 2017, our board of directors and stockholder, respectively, approved our 2017 Employee Stock Purchase Plan, or 2017 ESPP, which became effective upon the completion of our IPO, and the reservation for issuance thereunder of 500,000 shares of common stock. In addition, the number of shares of common stock that may be issued under the ESPP will automatically increase commencing on January 1, 2018 and ending on (and including) January 1, 2027 in an amount equal to the lesser of (i) 1% of the total number of shares of Common Stock outstanding on December 31st of the preceding calendar year, and (ii) 500,000 shares of Common Stock. On January 1, 2018, 500,000 shares of common stock were added to the ESPP.

As of December 31, 2018, the aggregate number of shares of common stock reserved under the 2017 ESPP was 1,000,000 and we had 968,449 shares available for future issuance under the 2017 ESPP. During the year ended December 31, 2018, 31,551 shares were issued under our 2017 ESPP. At December 31, 2018, accrued liabilities included $0.4 million of ESPP contributions for which the related shares were issued on January 1, 2019.

Stock Option Activity

The following table summarizes the stock option activity for the year ended December 31, 2018 (in thousands, except per share and contractual life data) for the 2015 Plan:

	Number of Shares	Weighted Average Exercise Price per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2017	7,905	$ 9.64		
Granted	4,833	$ 22.86		
Exercised	(835)	$ 7.98		
Cancelled/forfeited/expired	(892)	$ 16.53		
Outstanding at December 31, 2018	11,011	$ 15.00	8.07	$ 167,184
Exercisable at December 31, 2018	4,305	$ 8.04	7.11	$ 95,124

The weighted-average estimated fair value of options granted were $18.29, $10.4 and $4.13 for the years ended December 31, 2018, 2017 and 2016, respectively. For the year ended December 31, 2017, no stock options were exercised. For the year ended December 31, 2018, 834,800 stock options were exercised. As of December 31, 2018, total unrecognized estimated non-cash stock-based compensation expense related to non-vested stock options was $60.5 million. We will adjust total unrecognized compensation cost for future forfeitures. We expect to recognize the cost of non-cash stock-based compensation expense related to non-vested stock options over a weighted average amortization period of 1.32 years.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2018, 2017 and 2016 (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Cost of sales - product	$ 160	$ —	$ —
Research and development expenses	9,435	8,630	4,576
Selling, general and administrative expenses	34,687	8,909	5,573
Total	$ 44,282	$ 17,539	$ 10,149

Determining Fair Value

Valuation. We measure stock-based compensation expense for equity-classified awards related to stock options and stock purchase rights under the ESPP at the grant date, based on the estimated fair value of the award and we recognize the expense over the employee's requisite service period.

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. The expected term of stock options granted represents the period of time that we expect them to be outstanding. We estimate the expected term of options granted based on actual and projected exercise patterns. We recognize compensation expense for stock options granted and stock purchase rights under the ESPP using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

In valuing our options, we make a number of assumptions, including the risk-free interest rate, expected dividend yield, expected volatility, expected term, rate of forfeitures and fair value of common stock. We considered the following factors in applying these assumptions:

Risk-Free Interest Rate. We determine the risk-free interest rate assumption based on the yields of U.S. Treasury securities with maturities that correspond to the term of the award.

Expected Dividend Yield. We assume a dividend yield of zero as we have not paid dividends in the past and do not expect to pay dividends on our common stock for the foreseeable future.

Expected Volatility. We do not have sufficient history to estimate the volatility of our common stock. We calculate expected volatility based on a blend of our historical volatility and reported data from selected publicly traded peer companies for which historical information is available. We plan to continue to use this blend to calculate our volatility until the historical volatility of our common stock is sufficient to measure expected volatility for future option grants.

Expected Term. The expected term estimates represent the period of time that we expect the options to be outstanding. As we do not have historical information, we use the simplified method for estimating the expected term. Under the simplified method we calculate the expected term as the average time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our exercise patterns.

Rate of Forfeiture. We estimate forfeitures based on Ionis' historical rates of forfeiture as we do not have similar historical information for ourselves. We and Ionis are engaged in similar businesses and we believe this is a good estimate of expected forfeitures. As we gain additional historical information, we will transition to using our historical forfeiture rate.

Fair Value of Common Stock. Prior to our IPO our board of directors estimated the fair value of our common stock considering, among other things, contemporaneous valuations of our common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants 2013 Practice Aid, Valuation of Privately-Held-Company Equity Securities Issued as Compensation. Subsequent to the IPO, we use the market closing price for our common stock on the date of grant as reported on Nasdaq to determine the fair value of our common stock on the date of grant.

For the years ended December 31, 2018, 2017 and 2016, we used the following weighted-average assumptions in our Black-Scholes calculations for stock option grants under our 2015 Equity Incentive Plan:

Employee Stock Options:

	Years Ended December 31,		
	2018	2017	2016
Risk-free interest rate	2.8%	1.9%	1.6%
Dividend yield	0.0%	0.0%	0.0%
Volatility	77.1%	79.5%	71.4%
Expected life	6.08 years	6.06 years	6.08 years

Board of Director Stock Options:

	Years Ended December 31,		
	2018	2017	2016
Risk-free interest rate	2.9%	1.9%	2.0%
Dividend yield	0.0%	0.0%	0.0%
Volatility	78.2%	79.4%	79.6%
Expected life	6.42 years	6.25 years	6.08 years

10. Income Taxes

Loss before income taxes is comprised of (in thousands):

	Years Ended December 31,		
	2018	2017 (as revised)	2016
United States	$ (218,794)	$ (108,691)	$ (83,217)
Foreign	(6,580)	(11,593)	—
Loss before income tax expense	$ (225,374)	$ (120,284)	$ (83,217)

The provision (benefit) for income taxes is comprised of (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Current:			
Federal	$ —	$ —	$ —
State	73	1,041	—
Foreign	374	234	—
Total current	447	1,275	—
Deferred:			
Federal	—	—	—
State	—	—	—
Foreign	—	—	—
Total deferred	—	—	—
Income tax expense	$ 447	$ 1,275	$ —

We recorded income tax expense of $0.4 million for the year ended December 31, 2018, which primarily consists of foreign income tax. We recorded income tax expense of $1.3 million for the year ended December 31, 2017, which primarily consists of state and foreign income tax. There is no provision for income taxes for the year ended December 31, 2016 because we have historically incurred net operating losses and we maintain a full valuation allowance against our net deferred tax assets.

The reconciliation between our effective tax rate on loss from continuing operations and the statutory U.S. tax rate is as follows (in thousands):

	Years Ended December 31,					
	2018		2017 (as revised)		2016	
Pre-tax loss	$ (225,374)		$ (120,284)		$ (83,217)	
Statutory rate	(47,329)	21.0%	(42,099)	35.0%	(29,126)	35.0%
State income tax net of federal benefit	(6,441)	2.9%	(2,371)	2.0%	(4,099)	4.9%
Impact of foreign tax rate differential	1,735	(0.8)%	4,072	(3.4)%	—	—
Net change in valuation allowance	54,173	(24.0)%	(18,917)	15.7%	43,438	(52.1)%
IP Transfer	(3,947)	1.8%				
Tax credits	(4,035)	1.8%	4,189	(3.5)%	(11,007)	13.2%
IPO/Deconsolidation adjustment	—	—	37,911	(31.5)%	—	—
Tax rate change	3,906	(1.7)%	19,046	(15.8)%	—	—
Nondeductible items and other	1,734	(0.9)%	(556)	0.5%	794	(1.0)%
Stock-based compensation	651	(0.3)%	—	—	—	—
Effective rate	$ 447	(0.2)%	$ 1,275	(1.0)%	$ —	—

Significant components of our deferred tax assets and liabilities as of December 31, 2017 and 2016 are as follows (in thousands):

	December 31,	
	2018	2017 (as revised)
Deferred Tax Assets:		
Net operating loss carryovers	$ 51,280	$ 1,157
Tax credits	31,768	29,334
Stock-based compensation	11,812	7,515
Deferred revenue	6,876	29,256
Intangible and capital assets	56,984	—
Other	1,996	240
Total deferred tax assets	$ 160,716	$ 67,502
Deferred Tax Liabilities:		
Fixed assets	(811)	(125)
Total deferred tax liabilities	$ (811)	$ (125)
Valuation allowance	(159,905)	(67,377)
Net deferred tax assets and liabilities	$ —	$ —

On December 22, 2017, the U.S. government enacted comprehensive tax legislation commonly referred to as the Tax Cuts and Jobs Act of 2017 (the "Tax Act"). The Tax Act created a new requirement on global intangible low-taxed income (“GILTI”) earned by foreign subsidiaries for tax years beginning on or after January 1, 2018. The GILTI provisions require foreign subsidiary earnings in excess of an allowable return on the foreign subsidiary’s assets to be included in our U.S. income tax return. Under U.S. GAAP, we are permitted to make an accounting policy election to either treat taxes due on future inclusions in U.S. taxable income related to GILTI as a current-period expense when incurred or to factor such amounts into our measurement of deferred taxes. We have made the election to account for GILTI as a component of current taxes incurred rather than as a component of deferred taxes.

Prior to the completion of our IPO we filed our tax returns on a consolidated and combined basis with Ionis for federal and state income tax purposes, respectively. For financial statement purposes when we are required to file on a consolidated or combined basis, we calculate our income tax amounts, including net operating losses and tax credit carryforwards, using a separate return methodology which determines income taxes as if we were a separate taxpayer from Ionis. Effective July 19, 2017, the date of our IPO, we are no longer included in the consolidated federal income tax return with Ionis.

We are still required to file most of our state tax returns on a consolidated or combined basis with Ionis. Therefore, for financial statement purposes we calculated our state income tax amounts using the separate return method. We have excluded from the deferred tax table above state net operating loss carryforwards (and the associated valuation allowance) that have been generated by Akcea on a separate company basis and utilized by Ionis in consolidated state tax return filings as the amounts represent hypothetical deferred tax assets which are not legally eligible to be utilized on tax returns by Akcea in future years.

At December 31, 2018, we had federal and state tax net operating loss carry forwards on a separate basis of $238.7 million and $4.2 million, respectively. $4.3 million of the federal net operating loss carry forwards will expire in 2034 and the remaining $234.4 million can be carried forward indefinitely. The state tax net operating loss carry forwards will begin to expire in 2029. We also have federal research and development tax credit carry forwards of $37.4 million that will begin to expire in 2034.

Utilization of the net operating loss carry forwards and credits may be subject to an annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

We record a valuation allowance to reduce the balance of our net deferred tax assets to the amount we believe is more-likely-than-not to be realized. We have incurred financial statement losses since inception and as a result we have a full valuation allowance recorded against our net deferred tax assets. We regularly assess the future realization of our net deferred tax assets and will reduce the valuation allowance in any such period in which we determine that all, or a portion, of our deferred tax assets are more-likely-than-not to be realized.

Our valuation allowance increased by $92.5 million from December 31, 2017 to December 31, 2018. The increase relates primarily to the net operating loss carryforward generated in 2018 and certain costs associated with the Inotersen transaction with Ionis which are capitalized and amortized for tax purposes.

Pursuant to the SEC Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act (“SAB 118”), a company may select between one of three scenarios to determine a reasonable estimate arising from the Tax Act. Those scenarios are (i) a final estimate which effectively closes the measurement window; (ii) a reasonable estimate leaving the measurement window open for future revisions; and (iii) no estimate as the law is still being analyzed. The Company was able to provide a reasonable estimate for the provisional revaluation of deferred taxes and the effects of the transition tax on undistributed foreign earnings and profits for the period ended December 31, 2017. During the quarter ended December 31, 2018 the Company completed its accounting for the impacts of the Tax Act and identified no material changes from its original analysis.

In February 2018, the FASB issued Accounting Standards Update No. 2018-02, Income Statement—Reporting Comprehensive Income (Topic 220): Reclassification of Certain Tax Effects from Accumulated Other Comprehensive Income (ASU 2018-02), which allows companies to reclassify stranded tax effects resulting from the Tax Act, from accumulated other comprehensive income to retained earnings. The new standard is effective for us beginning January 1, 2019, with early adoption permitted. We elected to early adopt the new standard at the beginning of the fourth quarter of 2018 using the aggregate portfolio approach. We elected not to reclassify the income tax effects of the Tax Act from AOCI to retained earnings.

We analyze our filing positions in all the U.S. federal, state and foreign jurisdictions where we are required to file income tax returns to determine if we have any uncertain tax positions on any income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize a tax benefit if the position has a less than 50 percent likelihood of being sustained upon examination.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Beginning balance of unrecognized tax benefits	$ 5,001	$ 5,012	$ 1,766
Additions related to the current year	691	1,723	3,246
Decreases related to prior year tax positions	(86)	(1,734)	—
Ending balance of unrecognized tax benefits	$ 5,606	$ 5,001	$ 5,012

We have unrecognized tax benefits of $5.6 million and $5.0 million for the years ended December 31, 2018 and 2017, respectively. Due to our valuation allowance, there are no unrecognized tax benefits at December 31, 2018 that would impact our effective tax rate, if recognized.

We do not foresee any material changes to our gross unrecognized tax benefits within the next twelve months.

We recognize interest and/or penalties related to income tax matters in income tax expense. We did not recognize any accrued interest and penalties related to gross unrecognized tax benefits during the year ended December 31, 2018, 2017 or 2016.

We are subject to taxation in the United States and various state and foreign jurisdictions. The tax years for 2014 through 2018 are subject to examination by the U.S. federal, state and foreign tax authorities.

We do not provide for a U.S. income tax liability and foreign withholding taxes on undistributed foreign earnings of our foreign subsidiaries as we consider those earnings to be permanently reinvested. The amount of unrecognized deferred tax liabilities associated with these earnings is immaterial.

11. Initial Public Offering

On July 19, 2017, we completed our IPO. Total net proceeds were $182.3 million, including the following:

- $132.3 million from the sale of 17,968,750 shares of our common stock in our IPO of which $25.0 million was invested by Ionis; and
- $50.0 million from the purchase of 6,250,000 shares by Novartis in a concurrent private placement.

In addition, both of the following occurred in connection with the completion of our IPO on July 19, 2017:

- the conversion of all outstanding shares of Series A convertible preferred stock into 28,884,540 shares of our common stock; and
- the conversion of $106.0 million of outstanding principal plus accrued interest from the line of credit into 13,438,339 shares of common stock.

12. Employment Benefits

We have an employee 401(k) salary deferral plan covering all employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit $18,500 and $24,500 in 2018 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $1.6 million, $0.3 million and $0.2 million in matching contributions for the years ended December 31, 2018, 2017 and 2016, respectively.

13. Basic and Diluted Net Loss Per Share

We issued 28,884,540 shares of Series A convertible preferred stock in December 2015. The Series A convertible preferred stock converted into common stock in conjunction with the IPO in July 2017. As a result there were 66,541,629 shares of common stock issued and outstanding and there were no longer any outstanding shares of Series A convertible preferred stock. We determined that the Series A convertible preferred stock was in substance common stock during the period that it was outstanding because the Series A convertible preferred stock was the lowest form of subordinated equity outstanding during that period and this class of stock would have been required to absorb the losses of the Company. Accordingly, we are using the two-class method for computing EPS.

In connection with the TTR License Agreement completed on April 17, 2018 with Ionis, we made distributions to Ionis representing the consideration to be paid in cash provided to Ionis in excess of the carrying value of the related assets acquired. These distributions are treated as dividends to Ionis; therefore, we have applied the two-class method loss per share to reflect the allocation of these distributions to the participating Ionis common shares.

The two-class method is an earnings allocation formula that determines loss per share for each class of common stock and participating security according to dividends declared (or accumulated) and participation rights in undistributed earnings. For the purposes of calculating loss per share under the two-class method, we have allocated the net loss between the Series A convertible preferred stock, common stock owned by Ionis and common stock owned by others.

Basic loss per share for each class of stock is computed by dividing total distributable losses applicable to Series A convertible preferred stock, common stock owned by Ionis and common stock owned by others, including the 6% cumulative dividend contractually due to Series A convertible preferred shareholders, by the weighted-average of preferred and common shares outstanding during the requisite period. The cumulative preferred stock dividend was not paid upon completion of the IPO because the IPO was not a liquidation event or a change in control. Prior to the IPO, the 6% cumulative Series A convertible preferred stock dividend was considered as required under the two-class method regardless of whether those dividends were actually distributed.

The following table summarizes the distributable losses for the years ended December 31, 2018, 2017 and 2016:

	Year Ended December 31,		
	2018	2017	2016
Net loss	$ (225,821)	$ (121,559)	$ (83,217)
Preferred stock dividend	—	(20,100)	—
Distributions to Ionis	(7,792)	—	—
Distributable losses	$ (233,613)	$ (141,659)	$ (83,217)

The following table summarizes the reconciliation of weighted-average shares outstanding used in the calculation of basic loss per share for the years ended December 31, 2018, 2017 and 2016:

	Year Ended December 31,		
Determination of shares:	2018	2017	2016
Weighted-average preferred shares outstanding	—	15,748,009	28,884,540
Weighted-average common shares outstanding owned by Ionis	59,812,394	20,669,446	—
Weighted-average common shares outstanding owned by others	21,553,407	9,593,322	—
Total weighted-average shares outstanding	81,365,801	46,010,777	28,884,540

The following table summarizes the calculation of basic loss per share for the years ended December 31, 2018, 2017 and 2016 (in thousands, except per share amounts):

	Year Ended December 31,		
	2018	2017	2016
Losses attributable to preferred shares	$ —	$ (48,485)	$ (83,217)
Less: Assumed dividend to preferred shares	—	20,100	—
Income (losses) allocated to preferred shares	—	(28,385)	(83,217)
Weighted-average preferred shares outstanding	—	15,748,009	28,884,540
Basic loss per preferred share	$ —	$ (1.80)	$ (2.88)
Losses allocated to Ionis	$ (171,730)	$ (63,638)	$ —
Plus: Distribution to Ionis	7,792	—	—
Losses available to Ionis	(163,938)	(63,638)	-
Weighted-average common shares outstanding owned by Ionis	59,812,394	20,669,446	—
Basic loss per common share owned by Ionis	$ (2.74)	$ (3.08)	$ —
Losses allocated to common shares owned by others	$ (61,883)	$ (29,536)	$ —
Weighted-average common shares outstanding owned by others	21,553,407	9,593,322	—
Basic loss per common share owned by others	$ (2.87)	$ (3.08)	$ —

For the years ended December 31, 2018, 2017 and 2016, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- Options to purchase common stock;
- Unvested restricted stock units; and
- Employee Stock Purchase Plan.

14. Contractual Obligations and Commitments

The following table summarizes the contractual obligations as of December 31, 2018 (in thousands):

		Payments due by period			
Year Ending December 31,	Total	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years
Operating lease obligations	$ 23,688	$ 2,308	$ 4,711	$ 4,805	$ 11,864
Purchase commitments	5,033	5,033	-	-	-
Total	$ 28,721	$ 7,341	$ 4,711	$ 4,805	$ 11,864

Operating Lease

On April 5, 2018, we entered into an operating lease agreement with MEPT Seaport 13 Stillings LLC, or MEPT, for 30,175 square feet of office space located in Boston, Massachusetts for our new corporate headquarters. The commencement date of the lease was August 2018 and the initial term of the lease is 123 months with one five-year renewal option. We took occupancy of the office space in Boston, Massachusetts in September 2018. MEPT is providing us with a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million. We provided MEPT with a letter of credit to secure our obligations under the lease in the initial amount of $2.4 million, to be reduced to $1.8 million on the third anniversary of the rent commencement date and to $1.2 million on the fifth anniversary of the rent commencement date if we meet certain conditions set forth in the lease at each such time. This balance is included in deposits and other assets on the accompanying consolidated balance sheets.

On November 12, 2018, we entered into an operating lease agreement with Ionis Pharmaceuticals to sublease 4,723 square feet of office space located in Carlsbad, California. The commencement date was March 2018 and the term of the lease is 64 months with a four-month free rent period.

Rent expense for the year ended December 31, 2018, 2017 and 2016 was $2.4 million, $0.7 million and $0.4 million, respectively. We recognize rent expense on a straight-line basis over the lease term for the lease of our office spaces, which resulted in a deferred rent balance of $4.8 million and $39,000 at December 31, 2018 and 2017, respectively.

Purchase Commitments

Purchase commitments include agreements to purchase goods or services that are enforceable and legally binding on us and that specify all significant terms, including, fixed or minimum quantities to be purchased; fixed, minimum or variable price provisions; and the approximate timing of the transaction. Such obligations are related principally to inventory purchase orders based on our current manufacturing needs and require significant lead times to be fulfilled by our vendors. Purchase commitments exclude agreements that are cancelable without penalty.

15. Restructuring

On September 6, 2018, we enacted a plan to reorganize our workforce to better align with the immediate needs of our business, the Reorganization Plan, following the August 27, 2018 announcement of the FDA's issuance of a Complete Response Letter for our New Drug Application for WAYLIVRA. In connection with the Reorganization Plan, we reduced our workforce by approximately 12%. The Reorganization Plan was approved by our board of directors on September 2, 2018, and affected employees were informed on September 6, 2018. The Reorganization Plan impacted U.S. team members primarily from the WAYLIVRA field team and functions focused principally on WAYLIVRA.

For the year ended December 31, 2018, we recorded $1.7 million of restructuring-related costs in operating expense including employee severance, benefits and related costs, net of adjustments for employees who forfeited part of their benefits. In addition, we also recorded $0.4 million of non-cash stock option modifications expenses related to the Reorganization Plan for the year ended December 31, 2018. We do not expect to incur any additional significant costs associated with this reorganization.

The following table summarizes the restructuring costs by category for the periods indicated (in thousands):

	Year Ended December 31, 2018			
	Cash	Adjustment	Non-Cash	Total
Research and development	$ 327	$ (34)	$ 209	$ 502
Selling, general and administrative	1,562	(116)	200	$ 1,646
Total	$ 1,889	$ (150)	$ 409	$ 2,148

The following table summarizes the restructuring reserve included in accrued compensation for the periods indicated (in thousands):

	Year Ended December 31, 2018
Restructuring reserve beginning balance	$ —
Restructuring expenses incurred during the period	1,889
Adjustments during the period	(150)
Amounts paid during the period	(1,696)
Restructuring reserve ending balance	$ 43

16. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2018 and 2017 are as follows (in thousands, except per share data):

2018 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Revenue:				
Commercial revenue:				
Product revenue	$ —	$ —	$ —	$ 2,237
Licensing revenue	—	—	12,000	—
Total commercial revenue	—	—	12,000	2,237
Research and development revenue under collaborative agreement	17,108	18,321	7,241	7,960
Total revenue	17,108	18,321	19,241	10,197
Expenses:				
Cost of sales - product	—	—	1,043	777
Cost of sales - intangible asset amortization	—	—	701	2,012
Cost of license	—	—	7,200	—
Research and development	27,970	39,457	29,381	33,532
Selling, general and administrative	19,465	42,287	45,924	45,934
Total expenses	47,435	81,744	84,249	82,255
Loss from operations	(30,327)	(63,423)	(65,008)	(72,058)
Other income (expense):				
Investment income	868	1,546	1,675	1,542
Interest expense	—	—	—	—
Other income (expense)	(168)	45	(25)	(41)
Loss before income tax expense	(29,627)	(61,832)	(63,358)	(70,557)
Income tax expense	—	(214)	(233)	—
Net loss	$ (29,627)	$ (62,046)	$ (63,591)	$ (70,557)
Net loss per share of preferred stock, basic and diluted	$ —	$ —	$ —	$ —
Weighted-average shares of preferred stock outstanding, basic and diluted	—	—	—	—
Net loss per share of common stock owned by Ionis, basic and diluted	$ (0.44)	$ (0.72)	$ (0.73)	$ (0.79)
Weighted-average shares of common stock outstanding owned by Ionis, basic and diluted	45,447,879	60,832,494	65,538,467	67,129,553
Net loss per share of common stock owned by others, basic and diluted	$ (0.44)	$ (0.85)	$ (0.73)	$ (0.79)
Weighted-average shares of common stock outstanding owned by others, basic and diluted	21,171,372	21,492,157	21,671,415	21,869,713

2017 Quarters	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
			(as revised)	
Revenue:				
Commercial revenue:				
Product revenue	$ —	$ —	$ —	$ —
Licensing revenue	—	—	—	—
Total commercial revenue	—	—	—	—
Research and development revenue under collaborative agreement	6,094	5,713	9,906	21,688
Total revenue	6,094	5,713	9,906	21,688
Expenses:				
Cost of sales - product	—	—	—	—
Cost of sales - intangible asset amortization	—	—	—	—
Cost of license	—	—	—	—
Research and development	64,794	18,487	17,640	25,968
Selling, general and administrative	4,676	6,915	8,373	17,018
Total expenses	69,470	25,402	26,013	42,986
Loss from operations	(63,376)	(19,689)	(16,107)	(21,298)
Other income (expense):				
Investment income	61	245	687	819
Interest expense	(541)	(965)	(224)	—
Other income (expense)	—	50	73	(19)
Loss before income tax expense	(63,856)	(20,359)	(15,571)	(20,498)
Income tax expense	—	—	(2,066)	791
Net loss	$ (63,856)	$ (20,359)	$ (17,637)	$ (19,707)
Net loss per share of preferred stock, basic and diluted	$ (2.21)	$ (0.70)	$ (0.01)	$ —
Weighted-average shares of preferred stock outstanding, basic and diluted	28,884,540	28,888,450	5,651,323	—
Net loss per share of common stock owned by Ionis, basic and diluted	$ —	$ —	$ (0.33)	$ (0.30)
Weighted-average shares of common stock outstanding owned by Ionis, basic and diluted	—	—	36,555,903	45,447,879
Net loss per share of common stock owned by others, basic and diluted	$ —	$ —	$ (0.33)	$ (0.30)
Weighted-average shares of common stock outstanding owned by others, basic and diluted	—	—	16,966,712	21,093,750

(1) We computed net loss per share independently for each of the quarters presented. Therefore, the sum of the quarterly net loss per share will not necessarily equal the total for the year.

(2) For the purposes of calculating EPS under the two-class method since our IPO in July 2017, we have allocated the net loss between the common stock and the Series A convertible preferred stock for the three-month period ended September 30, 2017. We determined it was appropriate to allocate losses to the Series A convertible preferred stock because it was the lowest form of subordinated equity during such period and because Ionis, the sole holder of the Series A convertible preferred stock, was

absorbing our losses during such period. Basic EPS for each class of stock is computed by dividing total distributable losses applicable to preferred and common stock, including the 6% cumulative dividend contractually due to Series A convertible preferred shareholders, by the weighted-average of preferred and common shares outstanding during the requisite period. The cumulative preferred stock dividend was not paid upon completion of the IPO because the IPO was not a liquidation event or a change in control. Prior to the IPO, the 6% cumulative Series A convertible preferred stock dividend was considered as required under the two-class method regardless of whether those dividends were actually distributed.

The following table summarizes the distributable losses for the quarter ended September 30, 2017 (in thousands):

	September 30, 2017 (as revised)
Net loss	$ (17,637)
Preferred stock dividend	(1,791)
Distributable losses	$ (19,428)

The following table summarizes the reconciliation of weighted-average shares outstanding used in the calculation of basic EPS for the quarter ended September 30, 2017:

	September 30, 2017
Determination of shares:	
Weighted-average preferred shares outstanding	5,651,323
Weighted-average common shares outstanding	53,522,615
Total weighted-average shares outstanding	59,173,938

The following table summarizes the calculation of basic EPS for the quarter ended September 30, 2017 (in thousands, except per share amounts):

	September 30, 2017 (as revised)
Losses attributable to preferred shares	$ (1,855)
Less: Assumed dividend to preferred shares	1,791
Income (losses) allocated to preferred shares	$ (64)
Weighted-average preferred shares outstanding	5,651,323
Basic income (loss) per preferred share	$ 0.01
Losses allocated to common shares	$ (17,573)
Weighted-average common shares outstanding	53,522,615
Basic loss per common share	$ (0.33)

(3) We did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been antidilutive.

17. Subsequent Events

AKCEA-APO(a)-L_{Rx} License Fee

On February 22, 2019, Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} as part of our strategic collaboration with Novartis discussed in Note 6, *Strategic Collaboration with Novartis*. As a result we earned a license fee of $150.0 million of which we will pay $75.0 million to Ionis as a sublicense fee. We will issue 2,837,373 shares of our common stock to Ionis as payment of the $75.0 million sublicense fee.

Exhibit 10.3

SUBLEASE

This Sublease (the "***Sublease***") is made and entered into as of November 12, 2018 ("***Effective Date***") between **Ionis Pharmaceuticals, Inc**., a Delaware corporation ("***Sublessor***"), with its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 and **Akcea Therapeutics, Inc**., a Delaware corporation ("***Subtenant***"), with its principal place of business at 22 Boston Wharf Road, 9th Floor, Boston, MA 02210.

1. **Premises**: In accordance with that certain Standard Industrial/Commercial Multi-Tenant Lease - Net dated January 25, 2018 between Sublessor and Landlord (defined below) ("***Prime Lease***"), Sublessor leases from SR22 Carlsbad I, LLC, a California limited liability company; APG Carlsbad I, LLC, a California limited liability company; and PRE IV C Oaks, LLC, a California limited liability company (collectively "***Landlord***") certain premises containing approximately 18,710 rentable square feet of industrial space in the approximate aggregate 156,977 square foot in the project known as Elevate located at 2870 Whiptail Loop, Suite 102, Carlsbad, CA 92010 ("***Leased Premises***"). The Leased Premises are further described in the Prime Lease, a copy of which is attached hereto as *Exhibit A* and is incorporated by reference herein.

2. **Demise:** In accordance with this Sublease, Sublessor hereby subleases to Subtenant, and Subtenant hereby subleases from Sublessor, 4,723 square feet of the Leased Premises ("Subleased Premises"). The actual Subleased Premises is located within that portion of the Leased Premises identified in yellow on *Exhibit B* attached hereto. Subject to the terms of the Prime Lease, at no additional charge to Subtenant (except such charges as may be included in the Common Area Operating Expenses in accordance with the terms of the Prime Lease, Subtenant shall have the right to use all associated common areas and shall have such other use and access rights as may be necessary for the exercise of its rights and the performance of its obligations hereunder, including, but not limited to, access to electrical, phone and data rooms, existing phone and data wiring infrastructure, and restrooms.

3. **Sublease**: This Sublease is subject and subordinate to the Prime Lease and to the matters to which the Prime Lease is or shall be subject and subordinate.

4. **Term:** The parties acknowledge and agree that Subtenant took possession of the premises on March 15, 2018, the usage of which was in accordance with the provisions of this Sublease. As such, for the purposes of this Agreement, the Sublease commenced on March 15, 2018 and shall expire on June 29, 2023 (the "Term"), unless sooner terminated in accordance with this Sublease.

5. **Prime Lease:** The Prime Lease is incorporated herein by reference so that, except to the extent that certain provisions of the Prime Lease are inapplicable or modified by this Sublease, or excluded below, each and every term, covenant and condition of the Prime Lease binding or inuring to the benefit of Landlord shall, in respect of the Sublease, bind or inure to the benefit of Sublessor, and each and every term, covenant and condition of the Prime Lease binding or inuring to the benefit of lessee thereunder shall, in respect to the Sublease, bind or inure to the benefit of Subtenant, with the same force and effect as if such terms, covenants and conditions were completely set forth in the Sublease, and as if the words "Lessor(s)" and "Lessee(s)", or words of similar import, wherever the same appear in the Prime Lease, were construed to mean, respectively, "Sublessor" and "Subtenant" in the Sublease, and as if the words "Leased Premises", "Premises", "Leased Property", or words of similar import, wherever the same appear in the Prime Lease, were construed to mean "Subleased Premises" in the Sublease, and as if the word "Lease", or words of similar import, wherever the same appear in the Prime Lease, were construed to mean the "Sublease."

If any of the express provisions of the Sublease shall conflict with any of the provisions of the Prime Lease incorporated by reference herein, such conflict shall be resolved in every instance in favor of the express provisions of the Sublease. Notwithstanding the foregoing or anything to the contrary contained herein, Subtenant shall not have the right to exercise any renewal options, expansion options, rights of first offer or similar rights set forth in the Prime Lease.

6. **Rent:** Subtenant shall pay a portion of the total rent paid by Sublessor, including base rent, additional costs and other charges (collectively referred to herein as "***Rent***") as set forth on *Exhibit C*. Subtenant shall make all payments to Sublessor at the address set forth herein or to such other place as Sublessor may designate in writing. If the Effective Date is other than the first day of a calendar month, the Rent for the first month shall be prorated and shall be tendered to Sublessor on the first day of the following calendar month.

7. **Performance by Sublessor:** Any obligations of Sublessor which are contained in the Sublease by the incorporation by reference of the provisions of the Prime Lease shall be observed or performed by Sublessor using reasonable efforts to cause the Landlord to observe and/or perform the same (which obligations include, without limitation, services to be provided by Landlord and restoration of damaged property), and Sublessor shall diligently enforce its rights to cause such observance or performance. Subtenant shall not in any event have any rights in respect of the Subleased Premises greater than Sublessor's right with respect thereto under the Prime Lease.

8. **No Breach of Prime Lease:** Subtenant shall not take any action or omission which may constitute (or be reasonably likely to lead to) a breach or violation of any term, covenant or condition of the Prime Lease by the lessee thereunder, whether or not such act or thing is permitted under the provisions of the Sublease. Sublessor shall not take any action or omission which may constitute (or be reasonably likely to lead to) a breach or violation of any term, covenant or condition of the Prime Lease.

9. **No Privity of Estate or Contract:** Nothing contained in the Sublease shall be construed to create privity of estate or of contract between Subtenant and the Landlord.

10. **Indemnity:** Subtenant shall indemnify and hold harmless Sublessor from any claims, liabilities and damages that Sublessor may sustain as a result of a breach by Subtenant of this Sublease. Sublessor shall indemnify and hold harmless Subtenant from any claims, liabilities and damages that Subtenant may sustain as a result of a breach by Sublessor of this Sublease.

11. **Releases:** Subtenant hereby releases Sublessor or anyone claiming through or under the Sublessor by way of subrogation or otherwise. Subtenant hereby releases the Landlord or anyone claiming through or under the Landlord by way of subrogation or otherwise to the extent that Sublessor, as tenant, released the Landlord pursuant to the terms of the Prime Lease, and/or the Landlord was relieved of liability or responsibility pursuant to the provisions of the Prime Lease. Subtenant will cause its insurance carriers to include any clauses or endorsements in favor of the Sublessor, Landlord and any additional parties which Sublessor is required to provide pursuant to the provisions of the Prime Lease with respect to the Subleased Premises.

12. **Use:** Subtenant shall use and occupy the Subleased Premises solely for general office purposes and lawful uses incidental thereto in accordance with the provisions of the Prime Lease. Any other activities not specifically mentioned above regarding the use and occupancy of the Subleased Premises are subject to the prior written approval of Sublessor and Landlord.

13. **Condition of Subleased Premises:** Subtenant is leasing the Subleased Premises in its "as is," "where is" condition on the date hereof. On or before the end of the Term of the Sublease, or earlier termination or expiration of this Sublease, Subtenant shall restore the Subleased Premises to the condition existing as of the commencement of the Term of the Sublease ordinary wear and tear excepted. The obligations of Subtenant hereunder shall survive the expiration or earlier termination of this Sublease.

14. **Consent and Approvals:** Sublessor shall reasonably cooperate to seek Landlord's consent to any matter under the Prime Lease as may be reasonably requested by Subtenant. Pursuant to the provisions of the Prime Lease, consent of the Landlord is not required for any assignment or sublease by Sublessor to a Lessee Affiliate as such term is defined in the Prime Lease.

15. **Notices:** Any notice, report, statement, approval, consent, designation, demand or request to be given under this Sublease shall be effective when made in writing, deposited for mailing with the United States Postal Service or with a recognized overnight delivery service and addressed to Sublessor or Subtenant at the following addresses:

Subtenant:	Akcea Therapeutics, Inc. 22 Boston Wharf Road, 9th Floor Boston, MA 02210 Attn: Chief Operating Officer
With an email copy to:	Akcea Therapeutics, Inc. 22 Boston Wharf Road, 9th Floor Boston, MA 02210 Attn: Vice President, Legal With an email copy to: legalnotices@akceatx.com
Sublessor:	Ionis Pharmaceuticals, Inc. 2855 Gazelle Court Carlsbad, CA 92010 Attn: Legal Department

With an email copy to: legalnotices@ionisph.com

Sublessor shall promptly give written notice to Subtenant of (i) all claims, demands or controversies by or with the Landlord under the Prime Lease and (ii) any events which require that Sublessor give notice to Landlord under the Prime Lease, which would materially affect Subtenant's rights or obligations hereunder.

16. **Termination:** If for any reason the Prime Lease shall terminate prior to the expiration of the Sublease Term, this Sublease shall thereupon be terminated and Sublessor shall have no liability whatsoever to Subtenant by reason thereof (unless the termination occurred as a result of Sublessor's default or breach under the Prime Lease.

17. **Assignment and Subletting**: Subtenant shall not sublet the Subleased Premises or any part thereof or assign the Sublease or otherwise encumber or dispose of its interest therein without Sublessor's and Landlord's prior written consent in each instance, which consent may be withheld in Sublessor's and/or Landlord's sole discretion.

18. **Insurance:** Subtenant shall, throughout the Term of this Sublease, maintain for the Subleased Premises comparable insurance coverage as required of Sublessor under the Prime Lease. Such insurance shall, in addition to complying with the requirements of the Prime Lease, name Sublessor as an additional insured.

19. **Default:** The default provisions set forth in the Prime Lease are incorporated herein by reference, *provided that* Subtenant shall have a five (5) day notice and cure period for monetary default and a thirty (30) day notice and cure period for non-monetary default (unless such non-monetary default is not capable of cure within thirty (30) days, in which case Subtenant shall have a reasonable period of time in which to effect a cure, so long as Subtenant diligently prosecutes the cure to completion). In addition, Subtenant shall be responsible for payment of any applicable late charges and fees as set forth in the Prime Lease arising out of any default by Subtenant.

20. **Brokerage**: Each party represents and warrants to the other that no broker or other person had any part, or was instrumental in any way, in bringing about the Sublease. Each party agrees to indemnify, defend and hold harmless the other from and against any claims made by any broker or other person for a brokerage commission, finder's fee, or similar compensation, by reason of or in connection with the Sublease, and any loss, liability, damage, cost and expense (including, without limitation, reasonable attorney's fees) which may be incurred in connection with such claims if such other broker or other person claims to have had dealings with such party.

21. **Waiver of Jury Trial and Right to Counterclaim:** Each party hereby waives all right to trial by jury in any action, proceeding or counterclaim arising out of or in any way connected with the Sublease, the relationship of Sublessor and Subtenant, the Subleased Premises and the use and occupancy thereof, and any claim of injury or damages.

22. **Modifications:** The Sublease cannot be changed orally or in any manner other than by a written agreement executed by both parties. Sublessor shall not amend the Prime Lease with respect to any material provision that would materially affect Subtenant's rights or obligations hereunder without Subtenant's prior written consent.

23. **Successors and Assigns:** The provisions of the Sublease, except as herein otherwise specifically provided, shall extend to, bind and inure to the benefit of the parties hereto and their respective personal representatives, heirs, successors and permitted assigns.

24. **Interpretation:** This Sublease shall be governed by and construed in accordance with the laws of the state in which the Subleased Premises are located. If any provision of the Sublease or application thereof to any person or circumstance shall, for any reason and to any extent, be invalid or unenforceable, the remainder of the Sublease and the application of that provision to other persons or circumstances shall not be affected but rather shall be enforced to the extent permitted by law. The captions and headings are solely for convenience of reference and shall be construed without regard to any presumption or other rule requiring construction against the party causing the Sublease to be drafted.

25. **Authority**: Each party represents and warrants that the undersigned has the full right, power and authority to execute this Sublease on behalf of the party indicated.

26. **Quiet Enjoyment:** Sublessor warrants that, upon payment of the Rent, as defined herein, and performance of all obligations, covenants and agreements of Subtenant hereunder, Subtenant shall peaceably and quietly have, hold and enjoy the Subleased Premises during the Sublease Term, subject however to the provisions of this Sublease.

27. **Parking:** Subject to the terms and conditions of the Prime Lease, Sublessor shall, at no cost to Subtenant, allow Subtenant the use of such parking as is made available to Sublessor under the Prime Lease with respect to the Subleased Premises.

28. **Counterparts:** This Sublease may be executed in multiple counterparts. A signed copy of this Sublease delivered either by facsimile or email shall be deemed to have the same legal effect as delivery of an original signed copy of this Sublease.

IN WITNESS WHEREOF, Sublessor and Subtenant have hereunto executed the Sublease as of the Effective Date.

SUBLESSOR:

By:	*/s/ Elizabeth L. Hougen*
Name:	Elizabeth L. Hougen
Date	December 21, 2018

SUBTENANT:

By:	/s/ Jeffrey M. Goldberg
Name:	Jeffrey M. Goldberg
Title	COO
Date	December 26, 2018

Exhibit A – Prime Lease

Exhibit B - Subleased Premises

Exhibit C – Rent Schedule

Exhibit A –Prime Lease

AIRCRE

STANDARD INDUSTRIAL/COMMERCIAL MULTI-TENANT LEASE - NET

1. **Basic Provisions ("Basic Provisions").**

1.1 **Parties.** This Lease ("Lease"), dated for reference purposes only January 25, 2018, is made by and between SB22 CARLSBAD OAKS DISTRIBUTION, LLC, a California limited liability company; APG CARLSBAD I, LLC, a California limited liability company; and PBE IV C OAKS, LLC, a California limited liability company (collectively "**Lessor**") and IONIS PHARMACEUTICALS, INC., a Delaware corporation ("**Lessee**"), (collectively the "**Parties**", or individually a "**Party**").

1.2(a) **Premises:** That certain real property, including all improvements therein or to be provided by Lessor under the terms of this Lease, commonly known as (street address, unit/suite, city, state): 2870 Whitetail Loop, Suite 102, Carlsbad, CA 92010 ("**Premises**"). The Premises are located in the County of San Diego, and are generally described as (describe briefly the nature of the Premises and the "**Project**"): An approximately 18,710 rentable square foot industrial space in an approximately 156,977 square foot project known as Elevate. In addition to Lessee's rights to use and occupy the Premises as hereinafter specified, Lessee shall have non-exclusive rights to any utility raceways of the building containing the Premises ("**Building**") and to the Common Areas (as defined in Paragraph 2.7 below), but shall not have any rights to the roof, or exterior walls of the Building or to any other buildings in the Project. The Premises, the Building, the Common Areas, the land upon which they are located, along with all other buildings and improvements thereon, are herein collectively referred to as the "**Project.**" (See also Paragraph 2)

1.2(b) **Parking:** 83 unreserved vehicle parking spaces. (See also Paragraph 2.6)

1.3 **Term:** five (5) years, ~~and~~ three (3) months and seventeen (17) days ("**Original Term**") commencing March 15, 2018 ("**Commencement Date**") and ending June 30, 2023 ("**Expiration Date**"). (See also Paragraph 3)

1.4 **Early Possession:** If the Premises are available Lessee may have non-exclusive possession of the Premises commencing upon full execution of this Lease, payment of monies due pursuant to Paragraph 1.7 and compliance with other provisions of the Lease. ("**Early Possession Date**"). (See also Paragraphs 3.2 and 3.3)

1.5 **Base Rent:** $20,196.00 per month ("**Base Rent**"), payable on the first day of each month commencing on the Commencement Date. (See also Paragraph 4)

☑ If this box is checked, there are provisions in this Lease for the Base Rent to be adjusted. See Paragraph 50.

1.6 **Lessee's Share of Common Area Operating Expenses:** eleven and 92/100 percent (11.92 %) ("**Lessee's Share**"). In the event that the size of the Premises and/or the Project are modified during the term of this Lease, Lessor shall recalculate Lessee's Share to reflect such modification.

1.7 **Base Rent and Other Monies Paid Upon Execution:**

(a) **Base Rent:** $20,196.00 for the period first calendar month of the term.

(b) **Common Area Operating Expenses:** $4,677.50 for the period first calendar month of the term.

(c) **Security Deposit:** $23,412.70 ("**Security Deposit**"). (See also Paragraph 5)

(d) **Other:** ~~_____ for _____~~.

(e) **Total Due Upon Execution of this Lease:** $48,286.20.

1.8 **Agreed Use:** Administrative office, warehouse and distribution for a pharmaceutical company. (See also Paragraph 6)

1.9 **Insuring Party.** Lessor is the "**Insuring Party**". (See also Paragraph 8)

1.10 **Real Estate Brokers.** (See also Paragraph 15 and 25)

(a) **Representation:** The following real estate brokers (the "**Brokers**") and brokerage relationships exist in this transaction (check applicable boxes):

☑ Cushman & Wakefield (Aric Starck and Dennis Visser) represents Lessor exclusively ("**Lessor's Broker**");

☑ CBRE(Roger Carlson) represents Lessee exclusively ("**Lessee's Broker**"); or

☐ _____ represents both Lessor and Lessee ("**Dual Agency**").

(b) **Payment to Brokers.** (See Paragraph 58) ~~Upon execution and delivery of this Lease by both Parties, Lessor shall pay to the Brokers the brokerage fee agreed to in a separate written agreement (or if there is no such agreement, the sum of _____ or _____% of the total Base Rent) for the brokerage services rendered by the Brokers.~~

1.11 **Guarantor.** The obligations of the Lessee under this Lease are to be guaranteed by N/A ("**Guarantor**"). (See also Paragraph 37)

1.12 **Attachments.** Attached hereto are the following, all of which constitute a part of this Lease:

☑ an Addendum consisting of Paragraphs 50 through 60;

☑ a site plan depicting the Premises (Exhibit A);

☐ a site plan depicting the Project;

☐ a current set of the Rules and Regulations for the Project;

☐ a current set of the Rules and Regulations adopted by the owners' association;

☐ a Work Letter;

☑ other (specify): Option(s) to Extend (Paragraph 61).

2. **Premises.**

2.1 **Letting.** Lessor hereby leases to Lessee, and Lessee hereby leases from Lessor, the Premises, for the term, at the rental, and upon all of the terms, covenants and conditions set forth in this Lease. While the approximate square footage of the Premises may have been used in the marketing of the Premises for purposes of comparison, the Base Rent stated herein is NOT tied to square footage and is not subject to adjustment should the actual size be determined to be different. **NOTE: Lessee is advised to verify the**

actual size prior to executing this Lease.

2.2 **Condition.** Lessor shall deliver that portion of the Premises contained within the Building ("**Unit**") to Lessee broom clean and free of debris on the Commencement Date or the Early Possession Date, whichever first occurs ("**Start Date**"), and, so long as the required service contracts described in Paragraph 7.1(b) below are obtained by Lessee and in effect within thirty days following the Start Date, warrants that the existing electrical, plumbing, fire sprinkler, lighting, heating, ventilating and air conditioning systems ("**HVAC**"), loading doors, sump pumps, if any, and all other such elements in the Unit, other than those constructed by Lessee, shall be in good operating condition on said date, that the structural elements of the roof, bearing walls and foundation of the Unit shall be free of material defects, and that the Unit does not contain hazardous levels of any mold or fungi defined as toxic under applicable state or federal law. If a non-compliance with such warranty exists as of the Start Date, or if one of such systems or elements should malfunction or fail within the appropriate warranty period, Lessor shall, as Lessor's sole obligation with respect to such matter, except as otherwise provided in this Lease, promptly after receipt of written notice from Lessee setting forth with specificity the nature and extent of such non-compliance, malfunction or failure, rectify same at Lessor's expense. The warranty periods shall be as follows: (i) 6 months as to the HVAC systems, and (ii) 30 days as to the remaining systems and other elements of the Unit. If Lessee does not give Lessor the required notice within the appropriate warranty period, correction of any such non-compliance, malfunction or failure shall be the obligation of Lessee at Lessee's sole cost and expense (except for the repairs to the fire sprinkler systems, roof, foundations, and/or bearing walls - see Paragraph 7). Lessor also warrants, that unless otherwise specified in writing, Lessor is unaware of (i) any recorded Notices of Default affecting the Premise; (ii) any delinquent amounts due under any loan secured by the Premises; and (iii) any bankruptcy proceeding affecting the Premises.

2.3 **Compliance.** Lessor warrants that to the best of its knowledge the improvements on the Premises comply with the building codes, applicable laws, covenants or restrictions of record, regulations, and ordinances ("**Applicable Requirements**") that were in effect at the time that each improvement, or portion thereof, was constructed. Said warranty does not apply to the use to which Lessee will put the Premises, modifications which may be required by the Americans with Disabilities Act or any similar laws as a result of Lessee's use (see Paragraph 49), or to any Alterations or Utility Installations (as defined in Paragraph 7.3(a)) made or to be made by Lessee. **NOTE: Lessee is responsible for determining whether or not the Applicable Requirements, and especially the zoning are appropriate for Lessee's intended use, and acknowledges that past uses of the Premises may no longer be allowed.** If the Premises do not comply with said warranty, Lessor shall, except as otherwise provided, promptly after receipt of written notice from Lessee setting forth with specificity the nature and extent of such non-compliance, rectify the same at Lessor's expense. If Lessee does not give Lessor written notice of a non-compliance with this warranty within 6 months following the Start Date, correction of that non-compliance shall be the obligation of Lessee at Lessee's sole cost and expense. If the Applicable Requirements are hereafter changed so as to require during the term of this Lease the construction of an addition to or an alteration of the Unit, Premises and/or Building, the remediation of any Hazardous Substance, or the reinforcement or other physical modification of the Unit, Premises and/or Building ("**Capital Expenditure**"), Lessor and Lessee shall allocate the cost of such work as follows:

(a) Subject to Paragraph 2.3(c) below, if such Capital Expenditures are required as a result of the specific and unique use of the Premises by Lessee as compared with uses by tenants in general, Lessee shall be fully responsible for the cost thereof, provided, however, that if such Capital Expenditure is required during the last 2 years of this Lease and the cost thereof exceeds 6 months' Base Rent, Lessee may instead terminate this Lease unless Lessor notifies Lessee, in writing, within 10 days after receipt of Lessee's termination notice that Lessor has elected to pay the difference between the actual cost thereof and the amount equal to 6 months' Base Rent. If Lessee elects termination, Lessee shall immediately cease the use of the Premises which requires such Capital Expenditure and deliver to Lessor written notice specifying a termination date at least 90 days thereafter. Such termination date shall, however, in no event be earlier than the last day that Lessee could legally utilize the Premises without commencing such Capital Expenditure.

(b) If such Capital Expenditure is not the result of the specific and unique use of the Premises by Lessee (such as, governmentally mandated seismic modifications), then Lessor shall pay for such Capital Expenditure and Lessee shall only be obligated to pay, each month during the remainder of the term of this Lease or any extension thereof, on the date that on which the Base Rent is due, an amount equal to 1/144th of the portion of such costs reasonably attributable to the Premises. Lessee shall pay Interest on the balance but may prepay its obligation at any time. If, however, such Capital Expenditure is required during the last 2 years of this Lease or if Lessor reasonably determines that it is not economically feasible to pay its share thereof, Lessor shall have the option to terminate this Lease upon 90 days prior written notice to Lessee unless Lessee notifies Lessor, in writing, within 10 days after receipt of Lessor's termination notice that Lessee will pay for such Capital Expenditure. If Lessor does not elect to terminate, and fails to tender its share of any such Capital Expenditure, Lessee may advance such funds and deduct same, with Interest, from Rent until Lessor's share of such costs have been fully paid. If Lessee is unable to finance Lessor's share, or if the balance of the Rent due and payable for the remainder of this Lease is not sufficient to fully reimburse Lessee on an offset basis, Lessee shall have the right to terminate this Lease upon 30 days written notice to Lessor.

(c) Notwithstanding the above, the provisions concerning Capital Expenditures are intended to apply only to non-voluntary, unexpected, and new Applicable Requirements. If the Capital Expenditures are instead triggered by Lessee as a result of an actual or proposed change in use, change in intensity of use, or modification to the Premises then, and in that event, Lessee shall either: (i) immediately cease such changed use or intensity of use and/or take such other steps as may be necessary to eliminate the requirement for such Capital Expenditure, or (ii) complete such Capital Expenditure at its own expense. Lessee shall not have any right to terminate this Lease.

2.4 **Acknowledgements.** Lessee acknowledges that: (a) it has been given an opportunity to inspect and measure the Premises, (b) it has been advised by Lessor and/or Brokers to satisfy itself with respect to the size and condition of the Premises (including but not limited to the electrical, HVAC and fire sprinkler systems, security, environmental aspects, and compliance with Applicable Requirements and the Americans with Disabilities Act), and their suitability for Lessee's intended use, (c) Lessee has made such investigation as it deems necessary with reference to such matters and assumes all responsibility therefor as the same relate to its occupancy of the Premises, (d) it is not relying on any representation as to the size of the Premises made by Brokers or Lessor, (e) the square footage of the Premises was not material to Lessee's decision to lease the Premises and pay the Rent stated herein, and (f) neither Lessor, Lessor's agents, nor Brokers have made any oral or written representations or warranties with respect to said matters other than as set forth in this Lease. In addition, Lessor acknowledges that: (i) Brokers have made no representations, promises or warranties concerning Lessee's ability to honor the Lease or suitability to occupy the Premises, and (ii) it is Lessor's sole responsibility to investigate the financial capability and/or suitability of all proposed tenants.

2.5 **Lessee as Prior Owner/Occupant.** The warranties made by Lessor in Paragraph 2 shall be of no force or effect if immediately prior to the Start Date Lessee was the owner or occupant of the Premises. In such event, Lessee shall be responsible for

any necessary corrective work.

2.6 **Vehicle Parking.** Lessee shall be entitled to use the number of Parking Spaces specified in Paragraph 1.2(b) on those portions of the Common Areas designated from time to time by Lessor for parking. Lessee shall not use more parking spaces than said number. Said parking spaces shall be used for parking by vehicles no larger than full-size passenger automobiles or pick-up trucks, herein called "**Permitted Size Vehicles.**" Lessor may regulate the loading and unloading of vehicles by adopting Rules and Regulations as provided in Paragraph 2.9. No vehicles other than Permitted Size Vehicles may be parked in the Common Area without the prior written permission of Lessor. In addition:

(a) Lessee shall not permit or allow any vehicles that belong to or are controlled by Lessee or Lessee's employees, suppliers, shippers, customers, contractors or invitees to be loaded, unloaded, or parked in areas other than those designated by Lessor for such activities.

(b) Lessee shall not service or store any vehicles in the Common Areas.

(c) If Lessee permits or allows any of the prohibited activities described in this Paragraph 2.6, then Lessor shall have the right, without notice, in addition to such other rights and remedies that it may have, to remove or tow away the vehicle involved and charge the cost to Lessee, which cost shall be immediately payable upon demand by Lessor.

2.7 **Common Areas - Definition.** The term "**Common Areas**" is defined as all areas and facilities outside the Premises and within the exterior boundary line of the Project and interior utility raceways and installations within the Unit that are provided and designated by the Lessor from time to time for the general non-exclusive use of Lessor, Lessee and other tenants of the Project and their respective employees, suppliers, shippers, customers, contractors and invitees, including parking areas, loading and unloading areas, trash areas, roofs, roadways, walkways, driveways and landscaped areas.

2.8 **Common Areas - Lessee's Rights.** Lessor grants to Lessee, for the benefit of Lessee and its employees, suppliers, shippers, contractors, customers and invitees, during the term of this Lease, the non-exclusive right to use, in common with others entitled to such use, the Common Areas as they exist from time to time, subject to any rights, powers, and privileges reserved by Lessor under the terms hereof or under the terms of any rules and regulations or restrictions governing the use of the Project. Under no circumstances shall the right herein granted to use the Common Areas be deemed to include the right to store any property, temporarily or permanently, in the Common Areas. Any such storage shall be permitted only by the prior written consent of Lessor or Lessor's designated agent, which consent may be revoked at any time. In the event that any unauthorized storage shall occur, then Lessor shall have the right, without notice, in addition to such other rights and remedies that it may have, to remove the property and charge the cost to Lessee, which cost shall be immediately payable upon demand by Lessor.

2.9 **Common Areas - Rules and Regulations.** Lessor or such other person(s) as Lessor may appoint shall have the exclusive control and management of the Common Areas and shall have the right, from time to time, to establish, modify, amend and enforce reasonable rules and regulations ("**Rules and Regulations**") for the management, safety, care, and cleanliness of the grounds, the parking and unloading of vehicles and the preservation of good order, as well as for the convenience of other occupants or tenants of the Building and the Project and their invitees. Lessee agrees to abide by and conform to all such Rules and Regulations, and shall use its best efforts to cause its employees, suppliers, shippers, customers, contractors and invitees to so abide and conform. Lessor shall not be responsible to Lessee for the non-compliance with said Rules and Regulations by other tenants of the Project.

2.10 **Common Areas - Changes.** Lessor shall have the right, in Lessor's sole discretion, from time to time:

(a) To make changes to the Common Areas, including, without limitation, changes in the location, size, shape and number of driveways, entrances, parking spaces, parking areas, loading and unloading areas, ingress, egress, direction of traffic, landscaped areas, walkways and utility raceways;

(b) To close temporarily any of the Common Areas for maintenance purposes so long as reasonable access to the Premises remains available;

(c) To designate other land outside the boundaries of the Project to be a part of the Common Areas;

(d) To add additional buildings and improvements to the Common Areas;

(e) To use the Common Areas while engaged in making additional improvements, repairs or alterations to the Project, or any portion thereof; and

(f) To do and perform such other acts and make such other changes in, to or with respect to the Common Areas and Project as Lessor may, in the exercise of sound business judgment, deem to be appropriate.

3. **Term.**

3.1 **Term.** The Commencement Date, Expiration Date and Original Term of this Lease are as specified in Paragraph 1.3.

3.2 **Early Possession.** Any provision herein granting Lessee Early Possession of the Premises is subject to and conditioned upon the Premises being available for such possession prior to the Commencement Date. Any grant of Early Possession only conveys a non-exclusive right to occupy the Premises. If Lessee totally or partially occupies the Premises prior to the Commencement Date, the obligation to pay Base Rent and Lessee's Share of Common Area Operating Expenses, Real Property Taxes and insurance premiums shall be abated for the period of such Early Possession. All other terms of this Lease (including but not limited to the obligations ~~to pay Lessee's Share of Common Area Operating Expenses, Real Property Taxes and insurance premiums and~~ to maintain the Premises) shall be in effect during such period. Any such Early Possession shall not affect the Expiration Date.

3.3 **Delay in Possession.** Lessor agrees to use its best commercially reasonable efforts to deliver possession of the Premises to Lessee by the Commencement Date. If, despite said efforts, Lessor is unable to deliver possession by such date, Lessor shall not be subject to any liability therefor, nor shall such failure affect the validity of this Lease or change the Expiration Date. Lessee shall not, however, be obligated to pay Rent or perform its other obligations until Lessor delivers possession of the Premises and any period of rent abatement that Lessee would otherwise have enjoyed shall run from the date of delivery of possession and continue for a period equal to what Lessee would otherwise have enjoyed under the terms hereof, but minus any days of delay caused by the acts or omissions of Lessee. If possession is not delivered within ~~90~~ 60 days after the Commencement Date, as the same may be extended under the terms of any Work Letter executed by Parties, Lessee may, at its option, by notice in writing within 10 days after the end of such ~~90~~ 60 day period, cancel this Lease, in which event the Parties shall be discharged from all obligations hereunder. If such written notice is not received by Lessor within said 10 day period, Lessee's right to cancel shall terminate. If possession of the Premises is not delivered within 120 days after the Commencement Date, this Lease shall terminate unless other agreements are reached between Lessor and Lessee, in writing.

3.4 **Lessee Compliance.** Lessor shall not be required to tender possession of the Premises to Lessee until Lessee complies with its obligation to provide evidence of insurance (Paragraph 8.5). Pending delivery of such evidence, Lessee shall be required to perform all of its obligations under this Lease from and after the Start Date, including the payment of Rent, notwithstanding Lessor's election to withhold possession pending receipt of such evidence of insurance. Further, if Lessee is required to perform any other

conditions prior to or concurrent with the Start Date, the Start Date shall occur but Lessor may elect to withhold possession until such conditions are satisfied.

4. Rent.

4.1 **Rent Defined.** All monetary obligations of Lessee to Lessor under the terms of this Lease (except for the Security Deposit) are deemed to be rent ("**Rent**"). All rent shall be payable to SR22 Carlsbad Oaks Distribution, LLC, at the address set forth below its signature to this Lease, unless changed in accordance with Paragraph 23.

4.2 **Common Area Operating Expenses.** Lessee shall pay to Lessor during the term hereof, in addition to the Base Rent, Lessee's Share (as specified in Paragraph 1.6) of all Common Area Operating Expenses, as hereinafter defined, during each calendar year of the term of this Lease, in accordance with the following provisions:

(a) "**Common Area Operating Expenses**" are defined, for purposes of this Lease, as all costs relating to the ownership and operation of the Project, including, but not limited to, the following:

(i) The operation, repair and maintenance, in neat, clean, good order and condition , and if necessary the replacement, of the following:

(aa) The Common Areas and Common Area Improvements, including parking areas, loading and unloading areas, trash areas, roadways, parkways, walkways, driveways, landscaped areas, bumpers, irrigation systems, Common Area lighting facilities, fences and gates, elevators, roofs, exterior walls of the buildings, building systems and roof drainage systems.

(bb) Exterior signs and any tenant directories.

(cc) Any fire sprinkler systems.

(dd) All other areas and improvements that are within the exterior boundaries of the Project but outside of the Premises and/or any other space occupied by a tenant.

(ii) The cost of water, gas, electricity and telephone to service the Common Areas and any utilities not separately metered.

(iii) The cost of trash disposal, pest control services, property management (equal to 3% of scheduled Base Rent, without giving effect to any abatements, and Lessee's Share of Common Area Operating Expenses), security services, owners' association dues and fees, the cost to repaint the exterior of any structures and the cost of any environmental inspections.

(iv) Reserves set aside for maintenance, repair and/or replacement of Common Area improvements and equipment.

(v) Real Property Taxes (as defined in Paragraph 10).

(vi) The cost of the premiums for the insurance maintained by Lessor pursuant to Paragraph 8.

(vii) Any deductible portion of an insured loss concerning the Building or the Common Areas.

(viii) Auditors', accountants' and attorneys' fees and costs related to the operation, maintenance, repair and replacement of the Project.

(ix) The cost of any capital improvement to the Building or the Project not covered under the provisions of Paragraph 2.3 provided; however, that Lessor shall allocate the cost of any such capital improvement over a 12 year period and Lessee shall not be required to pay more than Lessee's Share of 1/144th of the cost of such capital improvement in any given month.

(x) The cost of any other services to be provided by Lessor that are stated elsewhere in this Lease to be a Common Area Operating Expense.

(b) Any Common Area Operating Expenses and Real Property Taxes that are specifically attributable to the Unit, the Building or to any other building in the Project or to the operation, repair and maintenance thereof, shall be allocated entirely to such Unit, Building, or other building. However, any Common Area Operating Expenses and Real Property Taxes that are not specifically attributable to the Building or to any other building or to the operation, repair and maintenance thereof, shall be equitably allocated by Lessor to all buildings in the Project.

(c) The inclusion of the improvements, facilities and services set forth in Subparagraph 4.2(a) shall not be deemed to impose an obligation upon Lessor to either have said improvements or facilities or to provide those services unless the Project already has the same, Lessor already provides the services, or Lessor has agreed elsewhere in this Lease to provide the same or some of them.

(d) Lessee's Share of Common Area Operating Expenses is payable monthly on the same day as the Base Rent is due hereunder. The amount of such payments shall be based on Lessor's estimate of the annual Common Area Operating Expenses. Within ~~60~~ 180 days after the expiration of each calendar year of the term ~~written request~~ (but not more than once each year) Lessor shall deliver to Lessee a reasonably detailed statement showing Lessee's Share of the actual Common Area Operating Expenses for the preceding year. If Lessee's payments during such year exceed Lessee's Share, Lessor shall credit the amount of such over-payment against Lessee's future payments or, if no future payments are remaining, Lessor shall pay to Lessee the amount of such overpayment within 10 days after delivery by Lessor to Lessee of the statement. If Lessee's payments during such year were less than Lessee's Share, Lessee shall pay to Lessor the amount of the deficiency within 10 days after delivery by Lessor to Lessee of the statement.

(e) Common Area Operating Expenses shall not include any expenses paid by any tenant directly to third parties, or as to which Lessor is otherwise reimbursed by any third party, other tenant, or insurance proceeds.

4.3 **Payment.** Lessee shall cause payment of Rent to be received by Lessor in lawful money of the United States, without offset or deduction (except as specifically permitted in this Lease), on or before the day on which it is due. All monetary amounts shall be rounded to the nearest whole dollar. In the event that any invoice prepared by Lessor is inaccurate such inaccuracy shall not constitute a waiver and Lessee shall be obligated to pay the amount set forth in this Lease. Rent for any period during the term hereof which is for less than one full calendar month shall be prorated based upon the actual number of days of said month. Payment of Rent shall be made to Lessor at its address stated herein or to such other persons or place as Lessor may from time to time designate in writing. Acceptance of a payment which is less than the amount then due shall not be a waiver of Lessor's rights to the balance of such Rent, regardless of Lessor's endorsement of any check so stating. In the event that any check, draft, or other instrument of payment given by Lessee to Lessor is dishonored for any reason, Lessee agrees to pay to Lessor the sum of $25 in addition to any Late Charge and Lessor, at its option, may require all future Rent be paid by cashier's check. Payments will be applied first to accrued late charges and attorney's fees, second to accrued interest, then to Base Rent and Common Area Operating Expenses, and any remaining amount to any other outstanding charges or costs.

5. **Security Deposit.** Lessee shall deposit with Lessor upon execution hereof the Security Deposit as security for Lessee's faithful

performance of its obligations under this Lease. If Lessee fails to pay Rent, or otherwise Defaults under this Lease, Lessor may use, apply or retain all or any portion of said Security Deposit for the payment of any amount already due Lessor, for Rents which will be due in the future, and/ or to reimburse or compensate Lessor for any liability, expense, loss or damage which Lessor may suffer or incur by reason thereof. If Lessor uses or applies all or any portion of the Security Deposit, Lessee shall within 10 days after written request therefor deposit monies with Lessor sufficient to restore said Security Deposit to the full amount required by this Lease. If the Base Rent increases during the term of this Lease, Lessee shall, upon written request from Lessor, deposit additional monies with Lessor so that the total amount of the Security Deposit shall at all times bear the same proportion to the increased Base Rent as the initial Security Deposit bore to the initial Base Rent. Should the Agreed Use be amended to accommodate a material change in the business of Lessee or to accommodate a sublessee or assignee, Lessor shall have the right to increase the Security Deposit to the extent necessary, in Lessor's reasonable judgment, to account for any increased wear and tear that the Premises may suffer as a result thereof. If a change in control of Lessee occurs during this Lease and following such change the financial condition of Lessee is, in Lessor's reasonable judgment, significantly reduced, Lessee shall deposit such additional monies with Lessor as shall be sufficient to cause the Security Deposit to be at a commercially reasonable level based on such change in financial condition. Lessor shall not be required to keep the Security Deposit separate from its general accounts. Within 90 days after the expiration or termination of this Lease, Lessor shall return that portion of the Security Deposit not used or applied by Lessor. Lessor shall upon written request provide Lessee with an accounting showing how that portion of the Security Deposit that was not returned was applied. No part of the Security Deposit shall be considered to be held in trust, to bear interest or to be prepayment for any monies to be paid by Lessee under this Lease. THE SECURITY DEPOSIT SHALL NOT BE USED BY LESSEE IN LIEU OF PAYMENT OF THE LAST MONTH'S RENT.

6. Use.

6.1 Use. Lessee shall use and occupy the Premises only for the Agreed Use, or any other legal use which is reasonably comparable thereto, and for no other purpose. Lessee shall not use or permit the use of the Premises in a manner that is unlawful, creates damage, waste or a nuisance, or that disturbs occupants of or causes damage to neighboring premises or properties. Other than service ~~guide, signal and seeing eye~~ dogs, Lessee shall not keep or allow in the Premises any pets, animals, birds, fish, or reptiles. Lessor shall not unreasonably withhold or delay its consent to any written request for a modification of the Agreed Use, so long as the same will not impair the structural integrity of the Building or the mechanical or electrical systems therein, and/or is not significantly more burdensome to the Project. If Lessor elects to withhold consent, Lessor shall within 7 days after such request give written notification of same, which notice shall include an explanation of Lessor's objections to the change in the Agreed Use.

6.2 **Hazardous Substances**.

(a) **Reportable Uses Require Consent.** The term "**Hazardous Substance**" as used in this Lease shall mean any product, substance, or waste whose presence, use, manufacture, disposal, transportation, or release, either by itself or in combination with other materials expected to be on the Premises, is either: (i) potentially injurious to the public health, safety or welfare, the environment or the Premises, (ii) regulated or monitored by any governmental authority, or (iii) a basis for potential liability of Lessor to any governmental agency or third party under any applicable statute or common law theory. Hazardous Substances shall include, but not be limited to, hydrocarbons, petroleum, gasoline, and/or crude oil or any products, by-products or fractions thereof. Lessee shall not engage in any activity in or on the Premises which constitutes a Reportable Use of Hazardous Substances without the express prior written consent of Lessor and timely compliance (at Lessee's expense) with all Applicable Requirements. "**Reportable Use**" shall mean (i) the installation or use of any above or below ground storage tank, (ii) the generation, possession, storage, use, transportation, or disposal of a Hazardous Substance that requires a permit from, or with respect to which a report, notice, registration or business plan is required to be filed with, any governmental authority, and/or (iii) the presence at the Premises of a Hazardous Substance with respect to which any Applicable Requirements requires that a notice be given to persons entering or occupying the Premises or neighboring properties. Notwithstanding the foregoing, Lessee may use any ordinary and customary materials reasonably required to be used in the normal course of the Agreed Use, ordinary office supplies (copier toner, liquid paper, glue, etc.) and common household cleaning materials, so long as such use is in compliance with all Applicable Requirements, is not a Reportable Use, and does not expose the Premises or neighboring property to any meaningful risk of contamination or damage or expose Lessor to any liability therefor. In addition, Lessor may condition its consent to any Reportable Use upon receiving such additional assurances as Lessor reasonably deems necessary to protect itself, the public, the Premises and/or the environment against damage, contamination, injury and/or liability, including, but not limited to, the installation (and removal on or before Lease expiration or termination) of protective modifications (such as concrete encasements) and/or increasing the Security Deposit.

(b) **Duty to Inform Lessor.** If Lessee knows, or has reasonable cause to believe, that a Hazardous Substance has come to be located in, on, under or about the Premises, other than as previously consented to by Lessor, Lessee shall immediately give written notice of such fact to Lessor, and provide Lessor with a copy of any report, notice, claim or other documentation which it has concerning the presence of such Hazardous Substance.

(c) **Lessee Remediation.** Lessee shall not cause or permit any Hazardous Substance to be spilled or released in, on, under, or about the Premises (including through the plumbing or sanitary sewer system) and shall promptly, at Lessee's expense, comply with all Applicable Requirements and take all investigatory and/or remedial action reasonably recommended, whether or not formally ordered or required, for the cleanup of any contamination of, and for the maintenance, security and/or monitoring of the Premises or neighboring properties, that was caused or materially contributed to by Lessee, or pertaining to or involving any Hazardous Substance brought onto the Premises during the term of this Lease, by or for Lessee, or its agents, employees or invitees, ~~any third party~~.

(d) **Lessee Indemnification.** Lessee shall indemnify, defend and hold Lessor, its agents, employees, lenders and ground lessor, if any, harmless from and against any and all loss of rents and/or damages, liabilities, judgments, claims, expenses, penalties, and attorneys' and consultants' fees arising out of or involving any Hazardous Substance brought onto the Premises by or for Lessee, or its agents, employees or invitees ~~any third party~~ (provided, however, that Lessee shall have no liability under this Lease with respect to underground migration of any Hazardous Substance under the Premises from areas outside of the Project not caused or contributed to by Lessee). Lessee's obligations shall include, but not be limited to, the effects of any contamination or injury to person, property or the environment created or suffered by Lessee, and the cost of investigation, removal, remediation, restoration and/or abatement, and shall survive the expiration or termination of this Lease. No termination, cancellation or release agreement entered into by Lessor and Lessee shall release Lessee from its obligations under this Lease with respect to Hazardous Substances, unless specifically so agreed by Lessor in writing at the time of such agreement.

(e) **Lessor Indemnification.** Except as otherwise provided in paragraph 8.7, Lessor and its successors and assigns shall indemnify, defend, reimburse and hold Lessee, its employees and lenders, harmless from and against any and all ~~environmental~~

damages, including the cost of remediation, liabilities, judgments, claims, expenses, penalties and attorneys' and consultants' fees which are suffered as a direct result of Hazardous Substances on the Premises prior to Lessee taking possession or which are caused by the gross negligence or willful misconduct of Lessor, its agents or employees. Lessor's obligations, as and when required by the Applicable Requirements, shall include, but not be limited to, the cost of investigation, removal, remediation, restoration and/or abatement, and shall survive the expiration or termination of this Lease.

(f) **Investigations and Remediations**. Lessor shall retain the responsibility and pay for any investigations or remediation measures required by governmental entities having jurisdiction with respect to the existence of Hazardous Substances on the Premises prior to the Lessee taking possession, unless such remediation measure is required as a result of Lessee's use (including "Alterations", as defined in paragraph 7.3(a) below) of the Premises, in which event Lessee shall be responsible for such payment. Lessee shall cooperate fully in any such activities at the request of Lessor, including allowing Lessor and Lessor's agents to have reasonable access to the Premises at reasonable times in order to carry out Lessor's investigative and remedial responsibilities.

(g) **Lessor Termination Option**. If a Hazardous Substance Condition (see Paragraph 9.1(e)) occurs during the term of this Lease, unless Lessee is legally responsible therefor (in which case Lessee shall make the investigation and remediation thereof required by the Applicable Requirements and this Lease shall continue in full force and effect, but subject to Lessor's rights under Paragraph 6.2(d) and Paragraph 13), Lessor may, at Lessor's option, either (i) investigate and remediate such Hazardous Substance Condition, if required, as soon as reasonably possible at Lessor's expense, in which event this Lease shall continue in full force and effect, or (ii) if the estimated cost to remediate such condition exceeds 12 times the then monthly Base Rent or $100,000, whichever is greater, give written notice to Lessee, within 30 days after receipt by Lessor of knowledge of the occurrence of such Hazardous Substance Condition, of Lessor's desire to terminate this Lease as of the date 60 days following the date of such notice. In the event Lessor elects to give a termination notice, Lessee may, within 10 days thereafter, give written notice to Lessor of Lessee's commitment to pay the amount by which the cost of the remediation of such Hazardous Substance Condition exceeds an amount equal to 12 times the then monthly Base Rent or $100,000, whichever is greater. Lessee shall provide Lessor with said funds or satisfactory assurance thereof within 30 days following such commitment. In such event, this Lease shall continue in full force and effect, and Lessor shall proceed to make such remediation as soon as reasonably possible after the required funds are available. If Lessee does not give such notice and provide the required funds or assurance thereof within the time provided, this Lease shall terminate as of the date specified in Lessor's notice of termination.

6.3 **Lessee's Compliance with Applicable Requirements**. Except as otherwise provided in this Lease, Lessee shall, at Lessee's sole expense, fully, diligently and in a timely manner, materially comply with all Applicable Requirements, the requirements of any applicable fire insurance underwriter or rating bureau, and the recommendations of Lessor's engineers and/or consultants which relate in any manner to the Premises, without regard to whether said Applicable Requirements are now in effect or become effective after the Start Date. Lessee shall, within 10 days after receipt of Lessor's written request, provide Lessor with copies of all permits and other documents, and other information evidencing Lessee's compliance with any Applicable Requirements specified by Lessor, and shall immediately upon receipt, notify Lessor in writing (with copies of any documents involved) of any threatened or actual claim, notice, citation, warning, complaint or report pertaining to or involving the failure of Lessee or the Premises to comply with any Applicable Requirements. Likewise, Lessee shall immediately give written notice to Lessor of: (i) any water damage to the Premises and any suspected seepage, pooling, dampness or other condition conducive to the production of mold; or (ii) any mustiness or other odors that might indicate the presence of mold in the Premises.

6.4 **Inspection; Compliance**. Lessor and Lessor's "**Lender**" (as defined in Paragraph 30) and consultants authorized by Lessor shall have the right to enter into Premises at any time, in the case of an emergency, and otherwise at reasonable times after reasonable notice, for the purpose of inspecting and/or testing the condition of the Premises and/or for verifying compliance by Lessee with this Lease. The cost of any such inspections shall be paid by Lessor, unless a violation of Applicable Requirements, or a Hazardous Substance Condition (see Paragraph 9.1) is found to exist or be imminent, or the inspection is requested or ordered by a governmental authority. In such case, Lessee shall upon request reimburse Lessor for the cost of such inspection, so long as such inspection is reasonably related to the violation or contamination. In addition, Lessee shall provide copies of all relevant material safety data sheets (**MSDS**) to Lessor within 10 days of the receipt of written request therefor. Lessee acknowledges that any failure on its part to allow such inspections or testing will expose Lessor to risks and potentially cause Lessor to incur costs not contemplated by this Lease, the extent of which will be extremely difficult to ascertain. Accordingly, should the Lessee fail to allow such inspections and/or testing in a timely fashion the Base Rent shall be automatically increased, without any requirement for notice to Lessee, by an amount equal to 10% of the then existing Base Rent or $100, whichever is greater for the remainder to the Lease. The Parties agree that such increase in Base Rent represents fair and reasonable compensation for the additional risk/costs that Lessor will incur by reason of Lessee's failure to allow such inspection and/or testing. Such increase in Base Rent shall in no event constitute a waiver of Lessee's Default or Breach with respect to such failure nor prevent the exercise of any of the other rights and remedies granted hereunder.

7. Maintenance; Repairs; Utility Installations; Trade Fixtures and Alterations.

7.1 **Lessee's Obligations.**

(a) **In General**. Subject to the provisions of Paragraph 2.2 (Condition), 2.3 (Compliance), 6.3 (Lessee's Compliance with Applicable Requirements), 7.2 (Lessor's Obligations), 9 (Damage or Destruction), and 14 (Condemnation), Lessee shall, at Lessee's sole expense, keep the Premises, Utility Installations (intended for Lessee's exclusive use, no matter where located), and Alterations in good order, condition and repair (whether or not the portion of the Premises requiring repairs, or the means of repairing the same, are reasonably or readily accessible to Lessee, and whether or not the need for such repairs occurs as a result of Lessee's use, any prior use, the elements or the age of such portion of the Premises), including, but not limited to, all equipment or facilities, such as plumbing, HVAC equipment, electrical, lighting facilities, boilers, pressure vessels, fixtures, interior walls, interior surfaces of exterior walls, ceilings, floors (including floor coverings), windows, doors, plate glass, and skylights but excluding any items which are the responsibility of Lessor pursuant to Paragraph 7.2. Lessee, in keeping the Premises in good order, condition and repair, shall exercise and perform good maintenance practices, specifically including the procurement and maintenance of the service contracts required by Paragraph 7.1(b) below. Lessee's obligations shall include restorations, replacements or renewals when necessary to keep the Premises and all improvements thereon or a part thereof in good order, condition and state of repair.

(b) **Service Contracts**. Lessee shall, at Lessee's sole expense, procure and maintain contracts, with copies to Lessor, in customary form and substance for, and with contractors specializing and experienced in the maintenance of the following equipment and improvements, if any, if and when installed on the Premises: (i) HVAC equipment, (ii) boiler and pressure vessels, and (iii) clarifiers. However, Lessor reserves the right, upon notice to Lessee, to procure and maintain any or all of such service contracts, and Lessee shall reimburse Lessor, upon demand, for the cost thereof.

(c) **Failure to Perform.** If Lessee fails to perform Lessee's obligations under this Paragraph 7.1, Lessor may enter upon the Premises after 10 days' prior written notice to Lessee (except in the case of an emergency, in which case no notice shall be required), perform such obligations on Lessee's behalf, and put the Premises in good order, condition and repair, and Lessee shall promptly pay to Lessor a sum equal to 115% of the cost thereof.

(d) **Replacement.** Subject to Lessee's indemnification of Lessor as set forth in Paragraph 8.7 below, and without relieving Lessee of liability resulting from Lessee's failure to exercise and perform good maintenance practices, if an item described in Paragraph 7.1(b) cannot be repaired other than at a cost which is in excess of 50% of the cost of replacing such item, then such item shall be replaced by Lessor, and the cost thereof shall be prorated between the Parties and Lessee shall only be obligated to pay, each month during the remainder of the term of this Lease, on the date on which Base Rent is due, an amount equal to the product of multiplying the cost of such replacement by a fraction, the numerator of which is one, and the denominator of which is 144 (ie. 1/144th of the cost per month). Lessee shall pay interest on the unamortized balance but may prepay its obligation at any time.

7.2 **Lessor's Obligations.** Subject to the provisions of Paragraphs 2.2 (Condition), 2.3 (Compliance), 4.2 (Common Area Operating Expenses), 6 (Use), 7.1 (Lessee's Obligations), 9 (Damage or Destruction) and 14 (Condemnation), Lessor, subject to reimbursement pursuant to Paragraph 4.2, shall keep in good order, condition and repair the foundations, exterior walls, structural condition of interior bearing walls, exterior roof, fire sprinkler system, Common Area fire alarm and/or smoke detection systems, fire hydrants, parking lots, walkways, parkways, driveways, landscaping, fences, signs and utility systems serving the Common Areas and all parts thereof, as well as providing the services for which there is a Common Area Operating Expense pursuant to Paragraph 4.2. Lessor shall not be obligated to paint the exterior or interior surfaces of exterior walls nor shall Lessor be obligated to maintain, repair or replace windows, doors or plate glass of the Premises.

7.3 **Utility Installations; Trade Fixtures; Alterations.**

(a) **Definitions.** The term "**Utility Installations**" refers to all floor and window coverings, air and/or vacuum lines, power panels, electrical distribution, security and fire protection systems, communication cabling, lighting fixtures, HVAC equipment, plumbing, and fencing in or on the Premises. The term "**Trade Fixtures**" shall mean Lessee's machinery and equipment that can be removed without doing material damage to the Premises. The term "**Alterations**" shall mean any modification of the improvements, other than Utility Installations or Trade Fixtures, whether by addition or deletion. "**Lessee Owned Alterations and/or Utility Installations**" are defined as Alterations and/or Utility Installations made by Lessee that are not yet owned by Lessor pursuant to Paragraph 7.4(a).

(b) **Consent.** Lessee shall not make any Alterations or Utility Installations to the Premises without Lessor's prior written consent. Lessee may, however, make non-structural Alterations or Utility Installations to the interior of the Premises (excluding the roof) without such consent but upon notice to Lessor, as long as they are not visible from the outside, do not involve puncturing, relocating or removing the roof or any existing walls, will not affect the electrical, plumbing, HVAC, and/or life safety systems, do not trigger the requirement for additional modifications and/or improvements to the Premises resulting from Applicable Requirements, such as compliance with Title 24, and/or life safety systems, and the cumulative cost thereof during this Lease as extended does not exceed a sum equal to 3 month's Base Rent in the aggregate or a sum equal to one month's Base Rent in any one year. Notwithstanding the foregoing, Lessee shall not make or permit any roof penetrations and/or install anything on the roof without the prior written approval of Lessor. Lessor may, as a precondition to granting such approval, require Lessee to utilize a contractor chosen and/or approved by Lessor. Any Alterations or Utility Installations that Lessee shall desire to make and which require the consent of the Lessor shall be presented to Lessor in written form with detailed plans. Consent shall be deemed conditioned upon Lessee's: (i) acquiring all applicable governmental permits, (ii) furnishing Lessor with copies of both the permits and the plans and specifications prior to commencement of the work, and (iii) compliance with all conditions of said permits and other Applicable Requirements in a prompt and expeditious manner. Any Alterations or Utility Installations shall be performed in a workmanlike manner with good and sufficient materials. Lessee shall promptly upon completion furnish Lessor with as-built plans and specifications. For work which costs an amount in excess of one month's Base Rent, Lessor may condition its consent upon Lessee providing a lien and completion bond in an amount equal to 150% of the estimated cost of such Alteration or Utility Installation and/or upon Lessee's posting an additional Security Deposit with Lessor.

(c) **Liens; Bonds.** Lessee shall pay, when due, all claims for labor or materials furnished or alleged to have been furnished to or for Lessee at or for use on the Premises, which claims are or may be secured by any mechanic's or materialmen's lien against the Premises or any interest therein. Lessee shall give Lessor not less than 10 days notice prior to the commencement of any work in, on or about the Premises, and Lessor shall have the right to post notices of non-responsibility. If Lessee shall contest the validity of any such lien, claim or demand, then Lessee shall, at its sole expense defend and protect itself, Lessor and the Premises against the same and shall pay and satisfy any such adverse judgment that may be rendered thereon before the enforcement thereof. If Lessor shall require, Lessee shall furnish a surety bond in an amount equal to 150% of the amount of such contested lien, claim or demand, indemnifying Lessor against liability for the same. If Lessor elects to participate in any such action, Lessee shall pay Lessor's attorneys' fees and costs.

7.4 **Ownership; Removal; Surrender; and Restoration.**

(a) **Ownership.** Subject to Lessor's right to require removal or elect ownership as hereinafter provided, all Alterations and Utility Installations made by Lessee shall be the property of Lessee, but considered a part of the Premises. Lessor may, at any time, elect in writing to be the owner of all or any specified part of the Lessee Owned Alterations and Utility Installations. Unless otherwise instructed per paragraph 7.4(b) hereof, all Lessee Owned Alterations and Utility Installations shall, at the expiration or termination of this Lease, become the property of Lessor and be surrendered by Lessee with the Premises.

(b) **Removal.** By delivery to Lessee of written notice from Lessor not earlier than 90 and not later than 30 days prior to the end of the term of this Lease, Lessor may require that any or all Lessee Owned Alterations or Utility Installations be removed by the expiration or termination of this Lease. Lessor may require the removal at any time of all or any part of any Lessee Owned Alterations or Utility Installations made without the required consent.

(c) **Surrender; Restoration.** Lessee shall surrender the Premises by the Expiration Date or any earlier termination date, with all of the improvements, parts and surfaces thereof broom clean and free of debris, and in good operating order, condition and state of repair, ordinary wear and tear excepted. "Ordinary wear and tear" shall not include any damage or deterioration that would have been prevented by good maintenance practice. Notwithstanding the foregoing, if the Lessee occupies the Premises for 12 months or less, then Lessee shall surrender the Premises in the same condition as delivered to Lessee on the Start Date with NO allowance for ordinary wear and tear. Lessee shall repair any damage occasioned by the installation, maintenance or removal of Trade Fixtures, Lessee owned Alterations and/or Utility Installations, furnishings, and equipment as well as the removal of any storage tank installed by or for Lessee. Lessee shall also remove from the Premises any and all Hazardous Substances brought onto

the Premises by or for Lessee, or its agents, employees or invitees ~~any third party~~ (except Hazardous Substances which were deposited via underground migration from areas outside of the Project) to the level specified in Applicable Requirements. Trade Fixtures shall remain the property of Lessee and shall be removed by Lessee. Any personal property of Lessee not removed on or before the Expiration Date or any earlier termination date shall be deemed to have been abandoned by Lessee and may be disposed of or retained by Lessor as Lessor may desire. The failure by Lessee to timely vacate the Premises pursuant to this Paragraph 7.4(c) without the express written consent of Lessor shall constitute a holdover under the provisions of Paragraph 26 below.

8. Insurance; Indemnity.

8.1 **Payment of Premiums.** The cost of the premiums for the insurance policies required to be carried by Lessor, pursuant to Paragraphs 8.2(b), 8.3(a) and 8.3(b), shall be a Common Area Operating Expense. Premiums for policy periods commencing prior to, or extending beyond, the term of this Lease shall be prorated to coincide with the corresponding Start Date or Expiration Date.

8.2 **Liability Insurance.**

(a) **Carried by Lessee.** Lessee shall obtain and keep in force a Commercial General Liability policy of insurance protecting Lessee and Lessor as an additional insured against claims for bodily injury, personal injury, owned/non-owned/hired auto liability and property damage based upon or arising out of the ownership, use, occupancy or maintenance of the Premises and all areas appurtenant thereto. Such insurance shall be on an occurrence basis providing single limit coverage in an amount not less than $1,000,000 per occurrence with an annual aggregate of not less than $2,000,000. Lessee shall add Lessor as an additional insured by means of an endorsement at least as broad as the Insurance Service Organization's "Additional Insured-Managers and ~~or~~ Lessors of Premises" Endorsement. The policy shall not contain any intra-insured exclusions as between insured persons or organizations, but shall include coverage for liability assumed under this Lease as an "**insured contract**" for the performance of Lessee's indemnity obligations under this Lease. The limits of said insurance shall not, however, limit the liability of Lessee nor relieve Lessee of any obligation hereunder. Lessee shall provide an endorsement on its liability policy(ies) which provides that its insurance shall be primary to and not contributory with any similar insurance carried by Lessor, whose insurance shall be considered excess insurance only.

(b) **Carried by Lessor.** Lessor shall maintain liability insurance as described in Paragraph 8.2(a), in addition to, and not in lieu of, the insurance required to be maintained by Lessee. Lessee shall not be named as an additional insured therein.

8.3 **Property Insurance - Building, Improvements and Rental Value.**

(a) **Building and Improvements.** Lessor shall obtain and keep in force a policy or policies of insurance in the name of Lessor, with loss payable to Lessor, any ground-lessor, and to any Lender insuring loss or damage to the Premises. The amount of such insurance shall be equal to the full insurable replacement cost of the Premises, as the same shall exist from time to time, or the amount required by any Lender, but in no event more than the commercially reasonable and available insurable value thereof. Lessee Owned Alterations and Utility Installations, Trade Fixtures, and Lessee's personal property shall be insured by Lessee not by Lessor. If the coverage is available and commercially appropriate, such policy or policies shall insure against all risks of direct physical loss or damage (except the perils of flood and/or earthquake unless required by a Lender), including coverage for debris removal and the enforcement of any Applicable Requirements requiring the upgrading, demolition, reconstruction or replacement of any portion of the Premises as the result of a covered loss. Said policy or policies shall also contain an agreed valuation provision in lieu of any coinsurance clause, waiver of subrogation, and inflation guard protection causing an increase in the annual property insurance coverage amount by a factor of not less than the adjusted U.S. Department of Labor Consumer Price Index for All Urban Consumers for the city nearest to where the Premises are located. If such insurance coverage has a deductible clause, the deductible amount shall not exceed $5,000 per occurrence.

(b) **Rental Value.** Lessor shall also obtain and keep in force a policy or policies in the name of Lessor with loss payable to Lessor and any Lender, insuring the loss of the full Rent for one year with an extended period of indemnity for an additional 180 days ("Rental Value insurance"). Said insurance shall contain an agreed valuation provision in lieu of any coinsurance clause, and the amount of coverage shall be adjusted annually to reflect the projected Rent otherwise payable by Lessee, for the next 12 month period.

(c) **Adjacent Premises.** Lessee shall pay for any increase in the premiums for the property insurance of the Building and for the Common Areas or other buildings in the Project if said increase is caused by Lessee's acts, omissions, use or occupancy of the Premises.

(d) **Lessee's Improvements.** Since Lessor is the Insuring Party, Lessor shall not be required to insure Lessee Owned Alterations and Utility Installations unless the item in question has become the property of Lessor under the terms of this Lease.

8.4 **Lessee's Property; Business Interruption Insurance; Worker's Compensation Insurance.**

(a) **Property Damage.** Lessee shall obtain and maintain insurance coverage on all of Lessee's personal property, Trade Fixtures, and Lessee Owned Alterations and Utility Installations. Such insurance shall be full replacement cost coverage with a deductible of not to exceed $75,000 ~~$1,000~~ per occurrence. The proceeds from any such insurance shall be used by Lessee for the replacement of personal property, Trade Fixtures and Lessee Owned Alterations and Utility Installations.

(b) **Business Interruption.** Lessee shall obtain and maintain loss of income and extra expense insurance in amounts as will reimburse Lessee for direct or indirect loss of earnings attributable to all perils commonly insured against by prudent lessees in the business of Lessee or attributable to prevention of access to the Premises as a result of such perils.

(c) **Worker's Compensation Insurance.** Lessee shall obtain and maintain Worker's Compensation Insurance in such amount as may be required by Applicable Requirements. Such policy shall include a 'Waiver of Subrogation' endorsement. Lessee shall provide Lessor with a copy of such endorsement along with the certificate of insurance or copy of the policy required by paragraph 8.5.

(d) **No Representation of Adequate Coverage.** Lessor makes no representation that the limits or forms of coverage of insurance specified herein are adequate to cover Lessee's property, business operations or obligations under this Lease.

8.5 **Insurance Policies.** Insurance required herein shall be by companies maintaining during the policy term a "General Policyholders Rating" of at least A-, VII, as set forth in the most current issue of "Best's Insurance Guide", or such other rating as may be required by a Lender. Lessee shall not do or permit to be done anything which invalidates the required insurance policies. Lessee shall, prior to the Start Date, deliver to Lessor certified copies of policies of such insurance or certificates with copies of the required endorsements evidencing the existence and amounts of the required insurance. No such policy shall be cancelable except after 10 days' prior written notice to Lessor in the event of nonpayment of premium. Additionally, within five (5) business days of receipt of any notice of cancellation of insurance, Lessee shall provide Lessor with a copy of such notice received from an insurer together with proof of replacement coverage that complies with the

insurance requirements of this Lease. ~~or subject to modification except after 30 days prior written notice to Lessor.~~ Lessee shall, at least 10 days prior to the expiration of such policies, furnish Lessor with evidence of renewals or "insurance binders" evidencing renewal thereof, or Lessor may increase his liability insurance coverage and charge the cost thereof to Lessee, which amount shall be payable by Lessee to Lessor upon demand. Such policies shall be for a term of at least one year, or the length of the remaining term of this Lease, whichever is less. If either Party shall fail to procure and maintain the insurance required to be carried by it, the other Party may, but shall not be required to, procure and maintain the same.

8.6 **Waiver of Subrogation.** Without affecting any other rights or remedies, Lessee and Lessor each hereby release and relieve the other, and waive their entire right to recover damages against the other, for loss of or damage to its property arising out of or incident to the perils required to be insured against herein. The effect of such releases and waivers is not limited by the amount of insurance carried or required, or by any deductibles applicable hereto. The Parties agree to have their respective property damage insurance carriers waive any right to subrogation that such companies may have against Lessor or Lessee, as the case may be, so long as the insurance is not invalidated thereby.

8.7 **Indemnity.** Except for Lessor's gross negligence or willful misconduct, Lessee shall indemnify, protect, defend and hold harmless the Premises, Lessor and its agents, Lessor's master or ground lessor, partners and Lenders, from and against any and all claims, loss of rents and/or damages, liens, judgments, penalties, attorneys' and consultants' fees, expenses and/or liabilities arising out of, involving, or in connection with, the use and/or occupancy of the Premises by Lessee. If any action or proceeding is brought against Lessor by reason of any of the foregoing matters, Lessee shall upon notice defend the same at Lessee's expense by counsel reasonably satisfactory to Lessor and Lessor shall cooperate with Lessee in such defense. Lessor need not have first paid any such claim in order to be defended or indemnified.

8.8 **Exemption of Lessor and its Agents from Liability.** Notwithstanding the negligence or breach of this Lease by Lessor or its agents, but without limiting Lessor's liability for any of its covenants, obligations or warranties expressly set forth in the Lease (nor any of Lessee's releases and waivers set forth in Paragraph 8.6), neither Lessor nor its agents shall be liable under any circumstances for: (i) injury or damage to the person or goods, wares, merchandise or other property of Lessee, Lessee's employees, contractors, invitees, customers, or any other person in or about the Premises, whether such damage or injury is caused by or results from fire, steam, electricity, gas, water or rain, indoor air quality, the presence of mold or from the breakage, leakage, obstruction or other defects of pipes, fire sprinklers, wires, appliances, plumbing, HVAC or lighting fixtures, or from any other cause, whether the said injury or damage results from conditions arising upon the Premises or upon other portions of the Building, or from other sources or places, (ii) any damages arising from any act or neglect of any other tenant of Lessor or from the failure of Lessor or its agents to enforce the provisions of any other lease in the Project, or (iii) injury to Lessee's business or for any loss of income or profit therefrom. Instead, it is intended that Lessee's sole recourse in the event of such damages or injury be to file a claim on the insurance policy(ies) that Lessee is required to maintain pursuant to the provisions of paragraph 8.

8.9 **Failure to Provide Insurance.** Lessee acknowledges that any failure on its part to obtain or maintain the insurance required herein will expose Lessor to risks and potentially cause Lessor to incur costs not contemplated by this Lease, the extent of which will be extremely difficult to ascertain. Accordingly, for any month or portion thereof that Lessee does not maintain the required insurance and/or does not provide Lessor with the required binders or certificates evidencing the existence of the required insurance, the Base Rent shall be automatically increased, without any requirement for notice to Lessee, by an amount equal to 10% of the then existing Base Rent or $100, whichever is greater. The parties agree that such increase in Base Rent represents fair and reasonable compensation for the additional risk/costs that Lessor will incur by reason of Lessee's failure to maintain the required insurance. Such increase in Base Rent shall in no event constitute a waiver of Lessee's Default or Breach with respect to the failure to maintain such insurance, prevent the exercise of any of the other rights and remedies granted hereunder, nor relieve Lessee of its obligation to maintain the insurance specified in this Lease.

9. **Damage or Destruction.**

9.1 **Definitions.**

(a) **"Premises Partial Damage"** shall mean damage or destruction to the improvements on the Premises, other than Lessee Owned Alterations and Utility Installations, which can reasonably be repaired in 6 3 months or less from receipt of insurance proceeds, ~~the date of the damage or destruction,~~ and the cost thereof does not exceed a sum equal to 6 month's Base Rent. Lessor shall notify Lessee in writing within 30 days from the date of the damage or destruction as to whether or not the damage is Partial or Total.

(b) **"Premises Total Destruction"** shall mean damage or destruction to the improvements on the Premises, other than Lessee Owned Alterations and Utility Installations and Trade Fixtures, which cannot reasonably be repaired in 6 3 months or less from receipt of insurance proceeds ~~the date of the damage or destruction~~ and/or the cost thereof exceeds a sum equal to 6 month's Base Rent. Lessor shall notify Lessee in writing within 30 days from the date of the damage or destruction as to whether or not the damage is Partial or Total.

(c) **"Insured Loss"** shall mean damage or destruction to improvements on the Premises, other than Lessee Owned Alterations and Utility Installations and Trade Fixtures, which was caused by an event required to be covered by the insurance described in Paragraph 8.3(a), and for which insurance proceeds are received (provided that the foregoing limitation shall not apply unless Lessor has maintained the required insurance coverage), less ~~irrespective of~~ any deductible amounts or coverage limits involved.

(d) **"Replacement Cost"** shall mean the cost to repair or rebuild the improvements owned by Lessor at the time of the occurrence to their condition existing immediately prior thereto, including demolition, debris removal and upgrading required by the operation of Applicable Requirements, and without deduction for depreciation.

(e) **"Hazardous Substance Condition"** shall mean the occurrence or discovery of a condition involving the presence of, or a contamination by, a Hazardous Substance, in, on, or under the Premises which requires restoration.

9.2 **Partial Damage - Insured Loss.** If a Premises Partial Damage that is an Insured Loss occurs, then Lessor shall, at Lessor's expense (if Lessor receives insurance proceeds, provided that the foregoing limitation shall not apply unless Lessor has maintained the required insurance coverage), repair such damage (but not Lessee's Trade Fixtures or Lessee Owned Alterations and Utility Installations) as soon as reasonably possible and this Lease shall continue in full force and effect; provided, however, that Lessee shall, at Lessor's election, make the repair of any damage or destruction the total cost to repair of which is $10,000 or less, and, in such event, Lessor shall make any applicable insurance proceeds available to Lessee on a reasonable basis for that purpose. Notwithstanding the foregoing, if the required insurance was not in force or the insurance proceeds are not

sufficient to effect such repair, the Insuring Party shall promptly contribute the shortage in proceeds as and when required to complete said repairs. In the event, however, such shortage was due to the fact that, by reason of the unique nature of the improvements, full replacement cost insurance coverage was not commercially reasonable and available, Lessor shall have no obligation to pay for the shortage in insurance proceeds or to fully restore the unique aspects of the Premises unless Lessee provides Lessor with the funds to cover same, or adequate assurance thereof, within 10 days following receipt of written notice of such shortage and request therefor. If Lessor receives said funds or adequate assurance thereof within said 10 day period, the party responsible for making the repairs shall complete them as soon as reasonably possible and this Lease shall remain in full force and effect. If such funds or assurance are not received, Lessor may nevertheless elect by written notice to Lessee within 10 days thereafter to: (i) make such restoration and repair as is commercially reasonable with Lessor paying any shortage in proceeds, in which case this Lease shall remain in full force and effect, or (ii) have this Lease terminate 30 days thereafter. Lessee shall not be entitled to reimbursement of any funds contributed by Lessee to repair any such damage or destruction. Premises Partial Damage due to flood or earthquake shall be subject to Paragraph 9.3, notwithstanding that there may be some insurance coverage, but the net proceeds of any such insurance shall be made available for the repairs if made by either Party.

9.3 **Partial Damage - Uninsured Loss.** If a Premises Partial Damage that is not an Insured Loss occurs, unless caused by a negligent or willful act of Lessee (in which event Lessee shall make the repairs at Lessee's expense), Lessor may either: (i) repair such damage as soon as reasonably possible at Lessor's expense (subject to reimbursement pursuant to Paragraph 4.2), in which event this Lease shall continue in full force and effect, or (ii) terminate this Lease by giving written notice to Lessee within 30 days after receipt by Lessor of knowledge of the occurrence of such damage. Such termination shall be effective 60 days following the date of such notice. In the event Lessor elects to terminate this Lease, Lessee shall have the right within 10 days after receipt of the termination notice to give written notice to Lessor of Lessee's commitment to pay for the repair of such damage without reimbursement from Lessor. Lessee shall provide Lessor with said funds or satisfactory assurance thereof within 30 days after making such commitment. In such event this Lease shall continue in full force and effect, and Lessor shall proceed to make such repairs as soon as reasonably possible after the required funds are available. If Lessee does not make the required commitment, this Lease shall terminate as of the date specified in the termination notice.

9.4 **Total Destruction.** Notwithstanding any other provision hereof, if a Premises Total Destruction occurs, this Lease shall terminate 60 days following such Destruction. If the damage or destruction was caused by the gross negligence or willful misconduct of Lessee, Lessor shall have the right to recover Lessor's damages from Lessee, except as provided in Paragraph 8.6.

9.5 **Damage Near End of Term.** If at any time during the last 6 months of this Lease there is damage for which the cost to repair exceeds one month's Base Rent, whether or not an Insured Loss, Lessor may terminate this Lease effective 60 days following the date of occurrence of such damage by giving a written termination notice to Lessee within 30 days after the date of occurrence of such damage. Notwithstanding the foregoing, if Lessee at that time has an exercisable option to extend this Lease or to purchase the Premises, then Lessee may preserve this Lease by, (a) exercising such option and (b) providing Lessor with any shortage in insurance proceeds (or adequate assurance thereof) needed to make the repairs on or before the earlier of (i) the date which is 10 days after Lessee's receipt of Lessor's written notice purporting to terminate this Lease, or (ii) the day prior to the date upon which such option expires. If Lessee duly exercises such option during such period and provides Lessor with funds (or adequate assurance thereof) to cover any shortage in insurance proceeds, Lessor shall, at Lessor's commercially reasonable expense, repair such damage as soon as reasonably possible and this Lease shall continue in full force and effect. If Lessee fails to exercise such option and provide such funds or assurance during such period, then this Lease shall terminate on the date specified in the termination notice and Lessee's option shall be extinguished.

9.6 **Abatement of Rent; Lessee's Remedies.**

(a) **Abatement.** In the event of Premises Partial Damage or Premises Total Destruction or a Hazardous Substance Condition for which Lessee is not responsible under this Lease, the Rent payable by Lessee for the period required for the repair, remediation or restoration of such damage shall be abated in proportion to the degree to which Lessee's use of the Premises is impaired, but not to exceed the proceeds received from the Rental Value insurance. All other obligations of Lessee hereunder shall be performed by Lessee, and Lessor shall have no liability for any such damage, destruction, remediation, repair or restoration except as provided herein.

(b) **Remedies.** If Lessor is obligated to repair or restore the Premises and does not commence, in a substantial and meaningful way, such repair or restoration within 90 days after such obligation shall accrue, Lessee may, at any time prior to the commencement of such repair or restoration, give written notice to Lessor and to any Lenders of which Lessee has actual notice, of Lessee's election to terminate this Lease on a date not less than 60 days following the giving of such notice. If Lessee gives such notice and such repair or restoration is not commenced within 30 days thereafter, this Lease shall terminate as of the date specified in said notice. If the repair or restoration is commenced within such 30 days, this Lease shall continue in full force and effect. "Commence" shall mean either the unconditional authorization of the preparation of the required plans, or the beginning of the actual work on the Premises, whichever first occurs.

9.7 **Termination; Advance Payments.** Upon termination of this Lease pursuant to Paragraph 6.2(g) or Paragraph 9, an equitable adjustment shall be made concerning advance Base Rent and any other advance payments made by Lessee to Lessor. Lessor shall, in addition, return to Lessee so much of Lessee's Security Deposit as has not been, or is not then required to be, used by Lessor.

9.8 **Waive Statutes.** Lessor and Lessee agree that the terms of the Lease shall govern the effect of any damage to or destruction of the Premises with respect to termination of this Lease and hereby waive the provisions of any present or future statute to the extent inconsistent herewith, including, but not limited to, Section 1932(2) and 1933(4) of the California Civil Code (as may be amended or supplemented from time to time).

10. Real Property Taxes.

10.1 **Definition.** As used herein, the term "**Real Property Taxes**" shall include any form of assessment; real estate, general, special, ordinary or extraordinary, or rental levy or tax (other than inheritance, personal income or estate taxes); improvement bond; and/or license fee imposed upon or levied against any legal or equitable interest of Lessor in the Project, Lessor's right to other income therefrom, and/or Lessor's business of leasing, by any authority having the direct or indirect power to tax and where the funds are generated with reference to the Project address. The term "Real Property Taxes" shall also include any tax, fee, levy, assessment or charge, or any increase therein: (i) imposed by reason of events occurring during the term of this Lease, including but not limited to, a change in the ownership of the Project, (ii) a change in the improvements thereon, and/or (iii) levied or assessed on machinery or equipment provided by Lessor to Lessee pursuant to this Lease. In calculating Real Property Taxes for any calendar

year, the Real Property Taxes for any real estate tax year shall be included in the calculation of Real Property Taxes for such calendar year based upon the number of days which such calendar year and tax year have in common.

10.2 **Payment of Taxes.** Except as otherwise provided in Paragraph 10.3, Lessor shall pay the Real Property Taxes applicable to the Project, and said payments shall be included in the calculation of Common Area Operating Expenses in accordance with the provisions of Paragraph 4.2.

10.3 **Additional Improvements.** Common Area Operating Expenses shall not include Real Property Taxes specified in the tax assessor's records and work sheets as being caused by additional Improvements placed upon the Project by other lessees or by Lessor for the exclusive enjoyment of such other lessees. Notwithstanding Paragraph 10.2 hereof, Lessee shall, however, pay to Lessor at the time Common Area Operating Expenses are payable under Paragraph 4.2, the entirety of any increase in Real Property Taxes if assessed solely by reason of Alterations, Trade Fixtures or Utility Installations placed upon the Premises by Lessee or at Lessee's request or by reason of any alterations or Improvements to the Premises made by Lessor subsequent to the execution of this Lease by the Parties.

10.4 **Joint Assessment.** If the Building is not separately assessed, Real Property Taxes allocated to the Building shall be an equitable proportion of the Real Property Taxes for all of the land and Improvements included within the tax parcel assessed, such proportion to be determined by Lessor from the respective valuations assigned in the assessor's work sheets or such other information as may be reasonably available. Lessor's reasonable determination thereof, in good faith, shall be conclusive.

10.5 **Personal Property Taxes.** Lessee shall pay prior to delinquency all taxes assessed against and levied upon Lessee Owned Alterations and Utility Installations, Trade Fixtures, furnishings, equipment and all personal property of Lessee contained in the Premises. When possible, Lessee shall cause its Lessee Owned Alterations and Utility Installations, Trade Fixtures, furnishings, equipment and all other personal property to be assessed and billed separately from the real property of Lessor. If any of Lessee's said property shall be assessed with Lessor's real property, Lessee shall pay Lessor the taxes attributable to Lessee's property within 10 days after receipt of a written statement setting forth the taxes applicable to Lessee's property.

11. Utilities and Services. Lessee shall pay for all water, gas, heat, light, power, telephone, trash disposal and other utilities and services supplied to the Premises, together with any taxes thereon. Notwithstanding the provisions of Paragraph 4.2, if at any time in Lessor's sole judgment, Lessor determines that Lessee is using a disproportionate amount of water, electricity or other commonly metered utilities, or that Lessee is generating such a large volume of trash as to require an increase in the size of the trash receptacle and/or an increase in the number of times per month that it is emptied, then Lessor may increase Lessee's Base Rent by an amount equal to such increased costs. There shall be no abatement of Rent and Lessor shall not be liable in any respect whatsoever for the inadequacy, stoppage, interruption or discontinuance of any utility or service due to riot, strike, labor dispute, breakdown, accident, repair or other cause beyond Lessor's reasonable control or in cooperation with governmental request or directions.

12. Assignment and Subletting.

12.1 **Lessor's Consent Required.**

(a) Lessee shall not voluntarily or by operation of law assign, transfer, mortgage or encumber (collectively, "**assign or assignment**") or sublet all or any part of Lessee's interest in this Lease or in the Premises without Lessor's prior written consent; provided that Lessor's consent shall not be required for any assignment or sublease between Lessor and any entity controlled by, controlling or under common control with Lessee (a "**Lessee Affiliate**").

(b) Unless Lessee, or a Lessee Affiliate controlling Lessee, is a corporation and its stock is publicly traded on a national stock exchange, a change in the control of Lessee (or such Lessee Affiliate) shall constitute an assignment requiring consent, provided that neither of the following transactions or series of transactions shall constitute an assignment requiring Lessor's consent: (i) an initial public offering of the stock of Lessee on a national exchange; or (ii) a merger, sale acquisition or other transfer of substantially all of Lessee's shares or assets which does not result in the Net Worth of Lessee being reduced in excess of the maximum amount permitted pursuant to Paragraph 12.1(c) below, as long as the surviving entity (if Lessee is not the surviving entity) assumes the Lessee's obligations under this Lease. Without limiting the foregoing, the ~~The~~ transfer, on a cumulative basis, of 50% ~~25%~~ or more of the voting control of Lessee (provided that reasonable restrictions placed on the transfer or Lessee's stock or voting control pursuant to a bona fide financing transaction shall not be considered a transfer of voting control for the purposes hereof) shall constitute a change in control for this purpose.

(c) The involvement of Lessee or its assets in any transaction, or series of transactions (by way of merger, sale, acquisition, financing, transfer, leveraged buy-out or otherwise), whether or not a formal assignment or hypothecation of this Lease or Lessee's assets occurs, which results or will result in a reduction of the Net Worth of Lessee by an amount greater than 25% of such Net Worth as it was represented at the time of the execution of this Lease or at the time of the most recent assignment to which Lessor has consented, or as it exists immediately prior to said transaction or transactions constituting such reduction, whichever was or is greater, shall be considered an assignment of this Lease to which Lessor may withhold its consent. "**Net Worth of Lessee**" shall mean the net worth of Lessee (excluding any guarantors) established under generally accepted accounting principles.

(d) An assignment or subletting without Lessor's consent as required herein shall, at Lessor's option, be a Default curable after notice per Paragraph 13.1(d), or a noncurable Breach without the necessity of any notice and grace period. If Lessor elects to treat such unapproved assignment or subletting as a noncurable Breach, Lessor may either: (i) terminate this Lease, or (ii) upon 30 days written notice, increase the monthly Base Rent to 110% of the Base Rent then in effect. Further, in the event of such Breach and rental adjustment, (i) the purchase price of any option to purchase the Premises held by Lessee shall be subject to similar adjustment to 110% of the price previously in effect, and (ii) all fixed and non-fixed rental adjustments scheduled during the remainder of the Lease term shall be increased to 110% of the scheduled adjusted rent.

(e) Lessee's remedy for any breach of Paragraph 12.1 by Lessor shall be limited to compensatory damages and/or injunctive relief.

(f) Lessor may reasonably withhold consent to a proposed assignment or subletting if Lessee is in Default at the time consent is requested.

(g) Notwithstanding the foregoing, allowing a de minimis portion of the Premises, ie. 20 square feet or less, to be used by a third party vendor in connection with the installation of a vending machine or payphone shall not constitute a subletting.

12.2 **Terms and Conditions Applicable to Assignment and Subletting.**

(a) Regardless of Lessor's consent, no assignment or subletting shall : (i) be effective without the express written

assumption by such assignee or sublessee of the obligations of Lessee under this Lease, (ii) release Lessee of any obligations hereunder, or (iii) alter the primary liability of Lessee for the payment of Rent or for the performance of any other obligations to be performed by Lessee.

(b) Lessor may accept Rent or performance of Lessee's obligations from any person other than Lessee pending approval or disapproval of an assignment. Neither a delay in the approval or disapproval of such assignment nor the acceptance of Rent or performance shall constitute a waiver or estoppel of Lessor's right to exercise its remedies for Lessee's Default or Breach.

(c) Lessor's consent to any assignment or subletting shall not constitute a consent to any subsequent assignment or subletting.

(d) In the event of any Default or Breach by Lessee, Lessor may proceed directly against Lessee, any Guarantors or anyone else responsible for the performance of Lessee's obligations under this Lease, including any assignee or sublessee, without first exhausting Lessor's remedies against any other person or entity responsible therefor to Lessor, or any security held by Lessor.

(e) Each request for consent to an assignment or subletting shall be in writing, accompanied by information relevant to Lessor's determination as to the financial and operational responsibility and appropriateness of the proposed assignee or sublessee, including but not limited to the intended use and/or required modification of the Premises, if any, together with a fee of $500 as consideration for Lessor's considering and processing said request. Lessee agrees to provide Lessor with such other or additional information and/or documentation as may be reasonably requested. (See also Paragraph 36)

(f) Any assignee of, or sublessee under, this Lease shall, by reason of accepting such assignment, entering into such sublease, or entering into possession of the Premises or any portion thereof, be deemed to have assumed and agreed to conform and comply with each and every term, covenant, condition and obligation herein to be observed or performed by Lessee during the term of said assignment or sublease, other than such obligations as are contrary to or inconsistent with provisions of an assignment or sublease to which Lessor has specifically consented to in writing.

(g) Lessor's consent to any assignment or subletting shall not transfer to the assignee or sublessee any Option granted to the original Lessee by this Lease unless such transfer is specifically consented to by Lessor in writing. (See Paragraph 39.2)

12.3 **Additional Terms and Conditions Applicable to Subletting.** The following terms and conditions shall apply to any subletting by Lessee of all or any part of the Premises and shall be deemed included in all subleases under this Lease whether or not expressly incorporated therein:

(a) Lessee hereby assigns and transfers to Lessor all of Lessee's interest in all Rent payable on any sublease, and Lessor may collect such Rent and apply same toward Lessee's obligations under this Lease; provided, however, that until a Breach shall occur in the performance of Lessee's obligations, Lessee may collect said Rent. In the event that the amount collected by Lessor exceeds Lessee's then outstanding obligations any such excess shall be refunded to Lessee. Lessor shall not, by reason of the foregoing or any assignment of such sublease, nor by reason of the collection of Rent, be deemed liable to the sublessee for any failure of Lessee to perform and comply with any of Lessee's obligations to such sublessee. Lessee hereby irrevocably authorizes and directs any such sublessee, upon receipt of a written notice from Lessor stating that a Breach exists in the performance of Lessee's obligations under this Lease, to pay to Lessor all Rent due and to become due under the sublease. Sublessee shall rely upon any such notice from Lessor and shall pay all Rents to Lessor without any obligation or right to inquire as to whether such Breach exists, notwithstanding any claim from Lessee to the contrary.

(b) In the event of a Breach by Lessee, Lessor may, at its option, require sublessee to attorn to Lessor, in which event Lessor shall undertake the obligations of the sublessor under such sublease from the time of the exercise of said option to the expiration of such sublease; provided, however, Lessor shall not be liable for any prepaid rents or security deposit paid by such sublessee to such sublessor or for any prior Defaults or Breaches of such sublessor.

(c) Any matter requiring the consent of the sublessor under a sublease shall also require the consent of Lessor.

(d) No sublessee shall further assign or sublet all or any part of the Premises without Lessor's prior written consent.

(e) Lessor shall deliver a copy of any notice of Default or Breach by Lessee to the sublessee, who shall have the right to cure the Default of Lessee within the grace period, if any, specified in such notice. The sublessee shall have a right of reimbursement and offset from and against Lessee for any such Defaults cured by the sublessee.

(f) Notwithstanding anything to the contrary herein, for an approved sublease of the entire Premises for the entire remainder of the term, if the Net Worth of the sublessee is equal to or greater than the Net Worth of Lessee, the Lessee shall be released from any obligations under the Lease that accrues after the effective date of the sublease.

13. Default; Breach; Remedies.

13.1 **Default; Breach.** A **"Default"** is defined as a failure by the Lessee to comply with or perform any of the terms, covenants, conditions or Rules and Regulations under this Lease. A **"Breach"** is defined as the occurrence of one or more of the following Defaults, and the failure of Lessee to cure such Default within any applicable grace period:

(a) The abandonment of the Premises; or the vacating of the Premises without providing a commercially reasonable level of security, or where the coverage of the property insurance described in Paragraph 8.3 is jeopardized as a result thereof, or without providing reasonable assurances to minimize potential vandalism.

(b) The failure of Lessee to make any payment of Rent or any Security Deposit required to be made by Lessee hereunder, whether to Lessor or to a third party, when due, to provide reasonable evidence of insurance or surety bond, or to fulfill any obligation under this Lease which endangers or threatens life or property, where such failure continues for a period of 3 business days following written notice to Lessee. THE ACCEPTANCE BY LESSOR OF A PARTIAL PAYMENT OF RENT OR SECURITY DEPOSIT SHALL NOT CONSTITUTE A WAIVER OF ANY OF LESSOR'S RIGHTS, INCLUDING LESSOR'S RIGHT TO RECOVER POSSESSION OF THE PREMISES.

(c) The failure of Lessee to allow Lessor and/or its agents access to the Premises or the commission of waste, act or acts constituting public or private nuisance, and/or an illegal activity on the Premises by Lessee, where such actions continue for a period of 3 business days following written notice to Lessee. In the event that Lessee commits waste, a nuisance or an illegal activity a second time then, the Lessor may elect to treat such conduct as a non-curable Breach rather than a Default.

(d) The failure by Lessee to provide (i) reasonable written evidence of compliance with Applicable Requirements, (ii) the service contracts, (iii) the rescission of an unauthorized assignment or subletting, (iv) an Estoppel Certificate or financial statements, (v) a requested subordination, (vi) evidence concerning any guaranty and/or Guarantor, (vii) any document requested under Paragraph 41, (viii) material safety data sheets (MSDS), or (ix) any other documentation or information which Lessor may reasonably require of Lessee under the terms of this Lease, where any such failure continues for a period of 10 days following written notice to Lessee.

(e) A Default by Lessee as to the terms, covenants, conditions or provisions of this Lease, or of the rules adopted under Paragraph 2.9 hereof, other than those described in subparagraphs 13.1(a), (b), (c) or (d), above, where such Default continues for a period of 30 days after written notice; provided, however, that if the nature of Lessee's Default is such that more than 30 days are reasonably required for its cure, then it shall not be deemed to be a Breach if Lessee commences such cure within said 30 day period and thereafter diligently prosecutes such cure to completion.

(f) The occurrence of any of the following events: (i) the making of any general arrangement or assignment for the benefit of creditors; (ii) becoming a "**debtor**" as defined in 11 U.S.C. § 101 or any successor statute thereto (unless, in the case of a petition filed against Lessee, the same is dismissed within 60 days); (iii) the appointment of a trustee or receiver to take possession of substantially all of Lessee's assets located at the Premises or of Lessee's interest in this Lease, where possession is not restored to Lessee within 30 days; or (iv) the attachment, execution or other judicial seizure of substantially all of Lessee's assets located at the Premises or of Lessee's interest in this Lease, where such seizure is not discharged within 30 days; provided, however, in the event that any provision of this subparagraph is contrary to any applicable law, such provision shall be of no force or effect, and not affect the validity of the remaining provisions.

(g) The discovery that any financial statement of Lessee or of any Guarantor given to Lessor was materially false.

(h) If the performance of Lessee's obligations under this Lease is guaranteed: (i) the death of a Guarantor, (ii) the termination of a Guarantor's liability with respect to this Lease other than in accordance with the terms of such guaranty, (iii) a Guarantor's becoming insolvent or the subject of a bankruptcy filing, (iv) a Guarantor's refusal to honor the guaranty, or (v) a Guarantor's breach of its guaranty obligation on an anticipatory basis, and Lessee's failure, within 60 days following written notice of any such event, to provide written alternative assurance or security, which, when coupled with the then existing resources of Lessee, equals or exceeds the combined financial resources of Lessee and the Guarantors that existed at the time of execution of this Lease.

13.2 **Remedies.** If Lessee fails to perform any of its affirmative duties or obligations, within 10 days after written notice (or in case of an emergency, without notice), Lessor may, at its option, perform such duty or obligation on Lessee's behalf, including but not limited to the obtaining of reasonably required bonds, insurance policies, or governmental licenses, permits or approvals. Lessee shall pay to Lessor an amount equal to 115% of the costs and expenses incurred by Lessor in such performance upon receipt of an invoice therefor. In the event of a Breach, Lessor may, with or without further notice or demand, and without limiting Lessor in the exercise of any right or remedy which Lessor may have by reason of such Breach:

(a) Terminate Lessee's right to possession of the Premises by any lawful means, in which case this Lease shall terminate and Lessee shall immediately surrender possession to Lessor. In such event Lessor shall be entitled to recover from Lessee: (i) the unpaid Rent which had been earned at the time of termination; (ii) the worth at the time of award of the amount by which the unpaid rent which would have been earned after termination until the time of award exceeds the amount of such rental loss that the Lessee proves could have been reasonably avoided; (iii) the worth at the time of award of the amount by which the unpaid rent for the balance of the term after the time of award exceeds the amount of such rental loss that the Lessee proves could be reasonably avoided; and (iv) any other amount necessary to compensate Lessor for all the detriment proximately caused by the Lessee's failure to perform its obligations under this Lease or which in the ordinary course of things would be likely to result therefrom, including but not limited to the cost of recovering possession of the Premises, expenses of reletting, including necessary renovation and alteration of the Premises, reasonable attorneys' fees, and that portion of any leasing commission paid by Lessor in connection with this Lease applicable to the unexpired term of this Lease. The worth at the time of award of the amount referred to in provision (iii) of the immediately preceding sentence shall be computed by discounting such amount at the discount rate of the Federal Reserve Bank of the District within which the Premises are located at the time of award plus one percent. Efforts by Lessor to mitigate damages caused by Lessee's Breach of this Lease shall not waive Lessor's right to recover any damages to which Lessor is otherwise entitled. If termination of this Lease is obtained through the provisional remedy of unlawful detainer, Lessor shall have the right to recover in such proceeding any unpaid Rent and damages as are recoverable therein, or Lessor may reserve the right to recover all or any part thereof in a separate suit. If a notice and grace period required under Paragraph 13.1 was not previously given, a notice to pay rent or quit, or to perform or quit given to Lessee under the unlawful detainer statute shall also constitute the notice required by Paragraph 13.1. In such case, the applicable grace period required by Paragraph 13.1 and the unlawful detainer statute shall run concurrently, and the failure of Lessee to cure the Default within the greater of the two such grace periods shall constitute both an unlawful detainer and a Breach of this Lease entitling Lessor to the remedies provided for in this Lease and/or by said statute.

(b) Continue the Lease and Lessee's right to possession and recover the Rent as it becomes due, in which event Lessee may sublet or assign, subject only to reasonable limitations. Acts of maintenance, efforts to relet, and/or the appointment of a receiver to protect the Lessor's interests, shall not constitute a termination of the Lessee's right to possession.

(c) Pursue any other remedy now or hereafter available under the laws or judicial decisions of the state wherein the Premises are located. The expiration or termination of this Lease and/or the termination of Lessee's right to possession shall not relieve Lessee from liability under any indemnity provisions of this Lease as to matters occurring or accruing during the term hereof or by reason of Lessee's occupancy of the Premises.

13.3 **Inducement Recapture.** Any agreement for free or abated rent or other charges, the cost of tenant improvements for Lessee paid for or performed by Lessor, or for the giving or paying by Lessor to or for Lessee of any cash or other bonus, inducement or consideration for Lessee's entering into this Lease, all of which concessions are hereinafter referred to as "**Inducement Provisions**," shall be deemed conditioned upon Lessee's full and faithful performance of all of the terms, covenants and conditions of this Lease. Upon Breach of this Lease by Lessee, any such Inducement Provision shall automatically be deemed deleted from this Lease and of no further force or effect, and any rent, other charge, bonus, inducement or consideration theretofore abated, given or paid by Lessor under such an Inducement Provision shall be immediately due and payable by Lessee to Lessor, notwithstanding any subsequent cure of said Breach by Lessee. The acceptance by Lessor of rent or the cure of the Breach which initiated the operation of this paragraph shall not be deemed a waiver by Lessor of the provisions of this paragraph unless specifically so stated in writing by Lessor at the time of such acceptance.

13.4 **Late Charges.** Lessee hereby acknowledges that late payment by Lessee of Rent will cause Lessor to incur costs not contemplated by this Lease, the exact amount of which will be extremely difficult to ascertain. Such costs include, but are not limited to, processing and accounting charges, and late charges which may be imposed upon Lessor by any Lender. Accordingly, if any Rent shall not be received by Lessor within 5 days after such amount shall be due, then, without any requirement for notice to Lessee, Lessee shall immediately pay to Lessor a one-time late charge equal to 10% of each such overdue amount or $100, whichever is greater. The parties hereby agree that such late charge represents a fair and reasonable estimate of the costs Lessor will incur by reason of such late payment. Acceptance of such late charge by Lessor shall in no event constitute a waiver of Lessee's Default or Breach with respect to such overdue amount, nor prevent the exercise of any of the other rights and remedies granted hereunder. In

the event that a late charge is payable hereunder, whether or not collected, for 3 consecutive installments of Base Rent, then notwithstanding any provision of this Lease to the contrary, Base Rent shall, at Lessor's option, become due and payable quarterly in advance.

13.5 **Interest.** Any monetary payment due Lessor hereunder, other than late charges, not received by Lessor, when due shall bear interest from the 31st day after it was due. The interest ("**Interest**") charged shall be computed at the rate of 10% per annum but shall not exceed the maximum rate allowed by law. Interest is payable in addition to the potential late charge provided for in Paragraph 13.4.

13.6 **Breach by Lessor.**

(a) **Notice of Breach.** Lessor shall not be deemed in breach of this Lease unless Lessor fails within a reasonable time to perform an obligation required to be performed by Lessor. For purposes of this Paragraph, a reasonable time shall in no event be ~~less~~ more than 30 days after receipt by Lessor, and any Lender whose name and address shall have been furnished to Lessee in writing for such purpose, of written notice specifying wherein such obligation of Lessor has not been performed; provided, however, that if the nature of Lessor's obligation is such that more than 30 days are reasonably required for its performance, then Lessor shall not be in breach if performance is commenced within such 30 day period and thereafter diligently pursued to completion.

(b) **Performance by Lessee on Behalf of Lessor.** In the event that neither Lessor nor Lender cures said breach within 30 days after receipt of said notice, or if having commenced said cure they do not diligently pursue it to completion, then Lessee may elect to cure said breach at Lessee's expense and offset from Rent the actual and reasonable cost to perform such cure, provided however, that such offset shall not exceed an amount equal to the greater of one month's Base Rent or the Security Deposit, reserving Lessee's right to reimbursement from Lessor for any such expense in excess of such offset. Lessee shall document the cost of said cure and supply said documentation to Lessor.

14. Condemnation. If the Premises or any portion thereof are taken under the power of eminent domain or sold under the threat of the exercise of said power (collectively "**Condemnation**"), this Lease shall terminate as to the part taken as of the date the condemning authority takes title or possession, whichever first occurs. If more than 10% of the floor area of the Unit, or more than 25% of the parking spaces is taken by Condemnation, Lessee may, at Lessee's option, to be exercised in writing within 10 days after Lessor shall have given Lessee written notice of such taking (or in the absence of such notice, within 10 days after the condemning authority shall have taken possession) terminate this Lease as of the date the condemning authority takes such possession. If Lessee does not terminate this Lease in accordance with the foregoing, this Lease shall remain in full force and effect as to the portion of the Premises remaining, except that the Base Rent shall be reduced in proportion to the reduction in utility of the Premises caused by such Condemnation. Condemnation awards and/or payments shall be the property of Lessor, whether such award shall be made as compensation for diminution in value of the leasehold, the value of the part taken, or for severance damages; provided, however, that Lessee shall be entitled to any compensation paid by the condemnor for Lessee's relocation expenses, loss of business goodwill and/or Trade Fixtures, without regard to whether or not this Lease is terminated pursuant to the provisions of this Paragraph. All Alterations and Utility Installations made to the Premises by Lessee, for purposes of Condemnation only, shall be considered the property of the Lessee and Lessee shall be entitled to any and all compensation which is payable therefor. In the event that this Lease is not terminated by reason of the Condemnation, Lessor shall repair any damage to the Premises caused by such Condemnation.

15. Brokerage Fees.

~~15.1 **Additional Commission.** In addition to the payments owed pursuant to Paragraph 1.10 above, Lessor agrees that: (a) if Lessee exercises any Option, (b) if Lessee or anyone affiliated with Lessee acquires from Lessor any rights to the Premises or other premises owned by Lessor and located within the Project, (c) if Lessee remains in possession of the Premises, with the consent of Lessor, after the expiration of this Lease, or (d) if Base Rent is increased, whether by agreement or operation of an escalation clause herein, then, Lessor shall pay Broker a fee in accordance with the fee schedule of the Brokers in effect at the time the Lease was executed.~~

~~15.2 **Assumption of Obligations.** Any buyer or transferee of Lessor's interest in this Lease shall be deemed to have assumed Lessor's obligation hereunder. Brokers shall be third party beneficiaries of the provisions of Paragraphs 1.10, 15, 22 and 31. If Lessor fails to pay to Brokers any amounts due as and for brokerage fees pertaining to this Lease when due, then such amounts shall accrue Interest. In addition, if Lessor fails to pay any amounts to Lessee's Broker when due, Lessee's Broker may send written notice to Lessor and Lessee of such failure and if Lessor fails to pay such amounts within 10 days after said notice, Lessee shall pay said monies to its Broker and offset such amounts against Rent. In addition, Lessee's Broker shall be deemed to be a third party beneficiary of any commission agreement entered into by and/or between Lessor and Lessor's Broker for the limited purpose of collecting any brokerage fee owed.~~

15.3 **Representations and Indemnities of Broker Relationships.** Lessee and Lessor each represent and warrant to the other that it has had no dealings with any person, firm, broker or finder (other than the Brokers, if any) in connection with this Lease, and that no one other than said named Brokers is entitled to any commission or finder's fee in connection herewith. Lessee and Lessor do each hereby agree to indemnify, protect, defend and hold the other harmless from and against liability for compensation or charges which may be claimed by any such unnamed broker, finder or other similar party by reason of any dealings or actions of the indemnifying Party, including any costs, expenses, attorneys' fees reasonably incurred with respect thereto.

16. Estoppel Certificates.

(a) Each Party (as "**Responding Party**") shall within 10 days after written notice from the other Party (the "**Requesting Party**") execute, acknowledge and deliver to the Requesting Party a statement in writing in form similar to the then most current "**Estoppel Certificate**" form published BY AIR CRE, plus such additional information, confirmation and/or statements as may be reasonably requested by the Requesting Party.

(b) If the Responding Party shall fail to execute or deliver the Estoppel Certificate within such 10 day period, the Requesting Party may execute an Estoppel Certificate stating that: (i) the Lease is in full force and effect without modification except as may be represented by the Requesting Party, (ii) there are no uncured defaults in the Requesting Party's performance, and (iii) if Lessor is the Requesting Party, not more than one month's rent has been paid in advance. Prospective purchasers and encumbrancers may rely upon the Requesting Party's Estoppel Certificate, and the Responding Party shall be estopped from denying the truth of the facts contained in said Certificate. In addition, Lessee acknowledges that any failure on its part to provide such an Estoppel Certificate will expose Lessor to risks and potentially cause Lessor to incur costs not contemplated by this Lease, the extent of which will be extremely difficult to ascertain. Accordingly, should the Lessee fail to execute and/or deliver a requested Estoppel Certificate in a timely fashion the monthly Base Rent shall be automatically increased, without any requirement for notice to Lessee, by an amount

equal to 10% of the then existing Base Rent or $100, whichever is greater for remainder of the Lease. The Parties agree that such increase in Base Rent represents fair and reasonable compensation for the additional risk/costs that Lessor will incur by reason of Lessee's failure to provide the Estoppel Certificate. Such increase in Base Rent shall in no event constitute a waiver of Lessee's Default or Breach with respect to the failure to provide the Estoppel Certificate nor prevent the exercise of any of the other rights and remedies granted hereunder.

(c) If Lessor desires to finance, refinance, or sell the Premises, or any part thereof, Lessee and all Guarantors shall within 10 days after written notice from Lessor deliver to any potential lender or purchaser designated by Lessor such financial statements as may be reasonably required by such lender or purchaser, including but not limited to Lessee's financial statements for the past 3 years. All such financial statements shall be received by Lessor and such lender or purchaser in confidence and shall be used only for the purposes herein set forth.

17. Definition of Lessor. The term "Lessor" as used herein shall mean the owner or owners at the time in question of the fee title to the Premises, or, if this is a sublease, of the Lessee's interest in the prior lease. In the event of a transfer of Lessor's title or interest in the Premises or this Lease, Lessor shall deliver to the transferee or assignee (in cash or by credit) any unused Security Deposit held by Lessor. Upon such transfer or assignment and delivery of the Security Deposit, as aforesaid, the prior Lessor shall be relieved of all liability with respect to the obligations and/or covenants under this Lease thereafter to be performed by the Lessor. Subject to the foregoing, the obligations and/or covenants in this Lease to be performed by the Lessor shall be binding only upon the Lessor as hereinabove defined.

18. Severability. The invalidity of any provision of this Lease, as determined by a court of competent jurisdiction, shall in no way affect the validity of any other provision hereof.

19. Days. Unless otherwise specifically indicated to the contrary, the word "days" as used in this Lease shall mean and refer to calendar days.

20. Limitation on Liability. The obligations of Lessor under this Lease shall not constitute personal obligations of Lessor, or its partners, members, directors, officers or shareholders, and Lessee shall look to the Premises, and to no other assets of Lessor, for the satisfaction of any liability of Lessor with respect to this Lease, and shall not seek recourse against Lessor's partners, members, directors, officers or shareholders, or any of their personal assets for such satisfaction.

21. Time of Essence. Time is of the essence with respect to the performance of all obligations to be performed or observed by the Parties under this Lease.

22. No Prior or Other Agreements; ~~Broker Disclaimer~~. This Lease contains all agreements between the Parties with respect to any matter mentioned herein, and no other prior or contemporaneous agreement or understanding shall be effective. ~~Lessor and Lessee each represents and warrants to the Brokers that it has made, and is relying solely upon, its own investigation as to the nature, quality, character and financial responsibility of the other Party to this Lease and as to the use, nature, quality and character of the Premises. Brokers have no responsibility with respect thereto or with respect to any default or breach hereof by either Party.~~

23. Notices.

23.1 **Notice Requirements.** All notices required or permitted by this Lease or applicable law shall be in writing and may be delivered in person (by hand or by courier) or may be sent by regular, certified or registered mail or U.S. Postal Service Express Mail, with postage prepaid, or by facsimile transmission, or by email, and shall be deemed sufficiently given if served in a manner specified in this Paragraph 23. The addresses noted adjacent to a Party's signature on this Lease shall be that Party's address for delivery or mailing of notices. Either Party may by written notice to the other specify a different address for notice, except that upon Lessee's taking possession of the Premises, the Premises shall constitute Lessee's address for notice. A copy of all notices to Lessor shall be concurrently transmitted to such party or parties at such addresses as Lessor may from time to time hereafter designate in writing. (See also Paragraph 60.)

23.2 **Date of Notice.** Any notice sent by registered or certified mail, return receipt requested, shall be deemed given on the date of delivery shown on the receipt card, or if no delivery date is shown, the postmark thereon. If sent by regular mail the notice shall be deemed given 72 hours after the same is addressed as required herein and mailed with postage prepaid. Notices delivered by United States Express Mail or overnight courier that guarantees next day delivery shall be deemed given 24 hours after delivery of the same to the Postal Service or courier. Notices delivered by hand, or transmitted by facsimile transmission or by email shall be deemed delivered upon actual receipt. If notice is received on a Saturday, Sunday or legal holiday, it shall be deemed received on the next business day.

24. Waivers.

(a) No waiver by Lessor of the Default or Breach of any term, covenant or condition hereof by Lessee, shall be deemed a waiver of any other term, covenant or condition hereof, or of any subsequent Default or Breach by Lessee of the same or of any other term, covenant or condition hereof. Lessor's consent to, or approval of, any act shall not be deemed to render unnecessary the obtaining of Lessor's consent to, or approval of, any subsequent or similar act by Lessee, or be construed as the basis of an estoppel to enforce the provision or provisions of this Lease requiring such consent.

(b) The acceptance of Rent by Lessor shall not be a waiver of any Default or Breach by Lessee. Any payment by Lessee may be accepted by Lessor on account of monies or damages due Lessor, notwithstanding any qualifying statements or conditions made by Lessee in connection therewith, which such statements and/or conditions shall be of no force or effect whatsoever unless specifically agreed to in writing by Lessor at or before the time of deposit of such payment.

(c) THE PARTIES AGREE THAT THE TERMS OF THIS LEASE SHALL GOVERN WITH REGARD TO ALL MATTERS RELATED THERETO AND HEREBY WAIVE THE PROVISIONS OF ANY PRESENT OR FUTURE STATUTE TO THE EXTENT THAT SUCH STATUTE IS INCONSISTENT WITH THIS LEASE.

25. Disclosures Regarding The Nature of a Real Estate Agency Relationship.

(a) When entering into a discussion with a real estate agent regarding a real estate transaction, a Lessor or Lessee should from the outset understand what type of agency relationship or representation it has with the agent or agents in the transaction. Lessor and Lessee acknowledge being advised by the Brokers in this transaction, as follows:

(i) *Lessor's Agent.* A Lessor's agent under a listing agreement with the Lessor acts as the agent for the Lessor only. A Lessor's agent or subagent has the following affirmative obligations: *To the Lessor:* A fiduciary duty of utmost care, integrity, honesty, and loyalty in dealings with the Lessor. *To the Lessee and the Lessor:* (a) Diligent exercise of reasonable skills and care in

performance of the agent's duties. (b) A duty of honest and fair dealing and good faith. (c) A duty to disclose all facts known to the agent materially affecting the value or desirability of the property that are not known to, or within the diligent attention and observation of, the Parties. An agent is not obligated to reveal to either Party any confidential information obtained from the other Party which does not involve the affirmative duties set forth above.

(ii) *Lessee's Agent*. An agent can agree to act as agent for the Lessee only. In these situations, the agent is not the Lessor's agent, even if by agreement the agent may receive compensation for services rendered, either in full or in part from the Lessor. An agent acting only for a Lessee has the following affirmative obligations. *To the Lessee*: A fiduciary duty of utmost care, integrity, honesty, and loyalty in dealings with the Lessee. *To the Lessee and the Lessor*: (a) Diligent exercise of reasonable skills and care in performance of the agent's duties. (b) A duty of honest and fair dealing and good faith. (c) A duty to disclose all facts known to the agent materially affecting the value or desirability of the property that are not known to, or within the diligent attention and observation of, the Parties. An agent is not obligated to reveal to either Party any confidential information obtained from the other Party which does not involve the affirmative duties set forth above.

(iii) *Agent Representing Both Lessor and Lessee*. A real estate agent, either acting directly or through one or more associate licenses, can legally be the agent of both the Lessor and the Lessee in a transaction, but only with the knowledge and consent of both the Lessor and the Lessee. In a dual agency situation, the agent has the following affirmative obligations to both the Lessor and the Lessee: (a) A fiduciary duty of utmost care, integrity, honesty and loyalty in the dealings with either Lessor or the Lessee. (b) Other duties to the Lessor and the Lessee as stated above in subparagraphs (i) or (ii). In representing both Lessor and Lessee, the agent may not without the express permission of the respective Party, disclose to the other Party that the Lessor will accept rent in an amount less than that indicated in the listing or that the Lessee is willing to pay a higher rent than that offered. The above duties of the agent in a real estate transaction do not relieve a Lessor or Lessee from the responsibility to protect their own interests. Lessor and Lessee should carefully read all agreements to assure that they adequately express their understanding of the transaction. A real estate agent is a person qualified to advise about real estate. If legal or tax advice is desired, consult a competent professional.

~~(b) Brokers have no responsibility with respect to any default or breach hereof by either Party. The Parties agree that no lawsuit or other legal proceeding involving any breach of duty, error or omission relating to this Lease may be brought against Broker more than one year after the Start Date and that the liability (including court costs and attorneys' fees), of any Broker with respect to any such lawsuit and/or legal proceeding shall not exceed the fee received by such Broker pursuant to this Lease; provided, however, that the foregoing limitation on each Broker's liability shall not be applicable to any gross negligence or willful misconduct of such Broker.~~

~~(c) Lessor and Lessee agree to identify to Brokers as "Confidential" any communication or information given Brokers that is considered by such Party to be confidential.~~

26. No Right To Holdover. Lessee has no right to retain possession of the Premises or any part thereof beyond the expiration or termination of this Lease. In the event that Lessee holds over, then the Base Rent shall be increased to 150% of the Base Rent applicable immediately preceding the expiration or termination. Holdover Base Rent shall be calculated on monthly basis. Nothing contained herein shall be construed as consent by Lessor to any holding over by Lessee.

27. Cumulative Remedies. No remedy or election hereunder shall be deemed exclusive but shall, wherever possible, be cumulative with all other remedies at law or in equity.

28. Covenants and Conditions; Construction of Agreement. All provisions of this Lease to be observed or performed by Lessee are both covenants and conditions. In construing this Lease, all headings and titles are for the convenience of the Parties only and shall not be considered a part of this Lease. Whenever required by the context, the singular shall include the plural and vice versa. This Lease shall not be construed as if prepared by one of the Parties, but rather according to its fair meaning as a whole, as if both Parties had prepared it.

29. Binding Effect; Choice of Law. This Lease shall be binding upon the parties, their personal representatives, successors and assigns and be governed by the laws of the State in which the Premises are located. Any litigation between the Parties hereto concerning this Lease shall be initiated in the county in which the Premises are located.

30. Subordination; Attornment; Non-Disturbance.

30.1 **Subordination.** This Lease and any Option granted hereby shall be subject and subordinate to any ground lease, mortgage, deed of trust, or other hypothecation or security device (collectively, "**Security Device**"), now or hereafter placed upon the Premises, to any and all advances made on the security thereof, and to all renewals, modifications, and extensions thereof. Lessee agrees that the holders of any such Security Devices (in this Lease together referred to as "**Lender**") shall have no liability or obligation to perform any of the obligations of Lessor under this Lease. Any Lender may elect to have this Lease and/or any Option granted hereby superior to the lien of its Security Device by giving written notice thereof to Lessee, whereupon this Lease and such Options shall be deemed prior to such Security Device, notwithstanding the relative dates of the documentation or recordation thereof.

30.2 **Attornment.** In the event that Lessor transfers title to the Premises, or the Premises are acquired by another upon the foreclosure or termination of a Security Device to which this Lease is subordinated (i) Lessee shall, subject to the non-disturbance provisions of Paragraph 30.3, attorn to such new owner, and upon request, enter into a new lease, containing all of the terms and provisions of this Lease, with such new owner for the remainder of the term hereof, or, at the election of the new owner, this Lease will automatically become a new lease between Lessee and such new owner, and (ii) Lessor shall thereafter be relieved of any further obligations hereunder and such new owner shall assume all of Lessor's obligations, except that such new owner shall not: (a) be liable for any act or omission of any prior lessor or with respect to events occurring prior to acquisition of ownership; (b) be subject to any offsets or defenses which Lessee might have against any prior lessor, (c) be bound by prepayment of more than one month's rent, or (d) be liable for the return of any security deposit paid to any prior lessor which was not paid or credited to such new owner.

30.3 **Non-Disturbance.** With respect to Security Devices entered into by Lessor after the execution of this Lease, Lessee's subordination of this Lease shall be subject to receiving a commercially reasonable non-disturbance agreement (a "**Non-Disturbance Agreement**") from the Lender which Non-Disturbance Agreement provides that Lessee's possession of the Premises, and this Lease, including any options to extend the term hereof, will not be disturbed so long as Lessee is not in Breach hereof and attorns to the record owner of the Premises. Further, within 60 days after the execution of this Lease, Lessor shall, if requested by Lessee, use its commercially reasonable efforts to obtain a Non-Disturbance Agreement from the holder of any pre-existing Security Device which is recorded against the Premises. In the event that Lessor is unable to provide the Non-Disturbance Agreement within said 60 days, then

Lessee may, at Lessee's option, directly contact Lender and attempt to negotiate for the execution and delivery of a Non-Disturbance Agreement.

30.4 **Self-Executing.** The agreements contained in this Paragraph 30 shall be effective without the execution of any further documents; provided, however, that, upon written request from Lessor or a Lender in connection with a sale, financing or refinancing of the Premises, Lessee and Lessor shall execute such further writings as may be reasonably required to separately document any subordination, attornment and/or Non-Disturbance Agreement provided for herein.

31. Attorneys' Fees. If any Party or Broker brings an action or proceeding involving the Premises whether founded in tort, contract or equity, or to declare rights hereunder, the Prevailing Party (as hereafter defined) in any such proceeding, action, or appeal thereon, shall be entitled to reasonable attorneys' fees. Such fees may be awarded in the same suit or recovered in a separate suit, whether or not such action or proceeding is pursued to decision or judgment. The term, "**Prevailing Party**" shall include, without limitation, a Party or Broker who substantially obtains or defeats the relief sought, as the case may be, whether by compromise, settlement, judgment, or the abandonment by the other Party or Broker of its claim or defense. The attorneys' fees award shall not be computed in accordance with any court fee schedule, but shall be such as to fully reimburse all attorneys' fees reasonably incurred. In addition, Lessor shall be entitled to attorneys' fees, costs and expenses incurred in the preparation and service of notices of Default and consultations in connection therewith, whether or not a legal action is subsequently commenced in connection with such Default or resulting Breach ($200 is a reasonable minimum per occurrence for such services and consultation).

32. Lessor's Access; Showing Premises; Repairs. Lessor and Lessor's agents shall have the right to enter the Premises at any time, in the case of an emergency, and otherwise at reasonable times after reasonable prior notice for the purpose of showing the same to prospective purchasers, lenders, appraisers, or tenants, and making such alterations, repairs, improvements or additions to the Premises as Lessor may deem necessary or desirable and the erecting, using and maintaining of utilities, services, pipes and conduits through the Premises and/or other premises as long as there is no material adverse effect on Lessee's use of the Premises. All such activities shall be without abatement of rent or liability to Lessee.

33. Auctions. Lessee shall not conduct, nor permit to be conducted, any auction upon the Premises without Lessor's prior written consent. Lessor shall not be obligated to exercise any standard of reasonableness in determining whether to permit an auction.

34. Signs. Lessor may place on the Premises ordinary "For Sale" signs at any time and ordinary "For Lease" signs during the last 6 months of the term hereof. ~~Except for ordinary "For Sublease" signs which may be placed only on the Premises,~~ Lessee shall not place any sign upon the Project without Lessor's prior written consent. All signs must comply with all Applicable Requirements.

35. Termination; Merger. Unless specifically stated otherwise in writing by Lessor, the voluntary or other surrender of this Lease by Lessee, the mutual termination or cancellation hereof, or a termination hereof by Lessor for Breach by Lessee, shall automatically terminate any sublease or lesser estate in the Premises; provided, however, that Lessor may elect to continue any one or all existing subtenancies. Lessor's failure within 10 days following any such event to elect to the contrary by written notice to the holder of any such lesser interest, shall constitute Lessor's election to have such event constitute the termination of such interest.

36. Consents. All requests for consent shall be in writing. Except as otherwise provided herein, wherever in this Lease the consent of a Party is required to an act by or for the other Party, such consent shall not be unreasonably withheld, conditioned or delayed. Lessor's actual reasonable costs and expenses (including but not limited to architects', attorneys', engineers' and other consultants' fees) incurred in the consideration of, or response to, a request by Lessee for any Lessor consent, including but not limited to consents to an assignment, a subletting or the presence or use of a Hazardous Substance, shall be paid by Lessee upon receipt of an invoice and supporting documentation therefor. Lessor's consent to any act, assignment or subletting shall not constitute an acknowledgment that no Default or Breach by Lessee of this Lease exists, nor shall such consent be deemed a waiver of any then existing Default or Breach, except as may be otherwise specifically stated in writing by Lessor at the time of such consent. The failure to specify herein any particular condition to Lessor's consent shall not preclude the imposition by Lessor at the time of consent of such further or other conditions as are then reasonable with reference to the particular matter for which consent is being given. In the event that either Party disagrees with any determination made by the other hereunder and reasonably requests the reasons for such determination, the determining party shall furnish its reasons in writing and in reasonable detail within 10 business days following such request.

37. Guarantor.

37.1 **Execution.** The Guarantors, if any, shall each execute a guaranty in the form most recently published BY AIR CRE.

37.2 **Default.** It shall constitute a Default of the Lessee if any Guarantor fails or refuses, upon request to provide: (a) evidence of the execution of the guaranty, including the authority of the party signing on Guarantor's behalf to obligate Guarantor, and in the case of a corporate Guarantor, a certified copy of a resolution of its board of directors authorizing the making of such guaranty, (b) current financial statements, (c) an Estoppel Certificate, or (d) written confirmation that the guaranty is still in effect.

38. Quiet Possession. Subject to payment by Lessee of the Rent and performance of all of the covenants, conditions and provisions on Lessee's part to be observed and performed under this Lease, Lessee shall have quiet possession and quiet enjoyment of the Premises during the term hereof.

39. Options. If Lessee is granted any option, as defined below, then the following provisions shall apply.

39.1 **Definition.** "**Option**" shall mean: (a) the right to extend or reduce the term of or renew this Lease or to extend or reduce the term of or renew any lease that Lessee has on other property of Lessor; (b) the right of first refusal or first offer to lease either the Premises or other property of Lessor; (c) the right to purchase, the right of first offer to purchase or the right of first refusal to purchase the Premises or other property of Lessor.

39.2 **Options Personal To Original Lessee.** Any Option granted to Lessee in this Lease is personal to the original Lessee, and cannot be assigned or exercised by anyone other than said original Lessee and only while the original Lessee is in full possession of the Premises and, if requested by Lessor, with Lessee certifying that Lessee has no intention of thereafter assigning or subletting.

39.3 **Multiple Options.** In the event that Lessee has any multiple Options to extend or renew this Lease, a later Option cannot be exercised unless the prior Options have been validly exercised.

39.4 **Effect of Default on Options.**

(a) Lessee shall have no right to exercise an Option: (i) during the period commencing with the giving of any notice of Default and continuing until said Default is cured, (ii) during the period of time any Rent is unpaid (without regard to whether notice thereof is given Lessee), (iii) during the time Lessee is in Breach of this Lease, or (iv) in the event that Lessee has been given 3 or

more notices of separate Default, whether or not the Defaults are cured, during the 12 month period immediately preceding the exercise of the Option.

(b) The period of time within which an Option may be exercised shall not be extended or enlarged by reason of Lessee's inability to exercise an Option because of the provisions of Paragraph 39.4(a).

(c) An Option shall terminate and be of no further force or effect, notwithstanding Lessee's due and timely exercise of the Option, if, after such exercise and prior to the commencement of the extended term or completion of the purchase, (i) Lessee fails to pay Rent for a period of 30 days after such Rent becomes due (without any necessity of Lessor to give notice thereof), or (ii) if Lessee commits a Breach of this Lease.

40. Security Measures. Lessee hereby acknowledges that the Rent payable to Lessor hereunder does not include the cost of guard service or other security measures, and that Lessor shall have no obligation whatsoever to provide same. Lessee assumes all responsibility for the protection of the Premises, Lessee, its agents and invitees and their property from the acts of third parties.

41. Reservations. Lessor reserves the right: (i) to grant, without the consent or joinder of Lessee, such easements, rights and dedications that Lessor deems necessary, (ii) to cause the recordation of parcel maps and restrictions, and (iii) to create and/or install new utility raceways, so long as such easements, rights, dedications, maps, restrictions, and utility raceways do not unreasonably interfere with the use of the Premises by Lessee. Lessee agrees to sign any documents reasonably requested by Lessor to effectuate such rights.

42. Performance Under Protest. If at any time a dispute shall arise as to any amount or sum of money to be paid by one Party to the other under the provisions hereof, the Party against whom the obligation to pay the money is asserted shall have the right to make payment "under protest" and such payment shall not be regarded as a voluntary payment and there shall survive the right on the part of said Party to institute suit for recovery of such sum. If it shall be adjudged that there was no legal obligation on the part of said Party to pay such sum or any part thereof, said Party shall be entitled to recover such sum or so much thereof as it was not legally required to pay. A Party who does not initiate suit for the recovery of sums paid "under protest" within 6 months shall be deemed to have waived its right to protest such payment.

43. Authority; Multiple Parties; Execution.

(a) If either Party hereto is a corporation, trust, limited liability company, partnership, or similar entity, each individual executing this Lease on behalf of such entity represents and warrants that he or she is duly authorized to execute and deliver this Lease on its behalf. Each Party shall, within 30 days after request, deliver to the other Party satisfactory evidence of such authority.

(b) If this Lease is executed by more than one person or entity as "Lessee", each such person or entity shall be jointly and severally liable hereunder. It is agreed that any one of the named Lessees shall be empowered to execute any amendment to this Lease, or other document ancillary thereto and bind all of the named Lessees, and Lessor may rely on the same as if all of the named Lessees had executed such document.

(c) This Lease may be executed by the Parties in counterparts, each of which shall be deemed an original and all of which together shall constitute one and the same instrument.

44. Conflict. Any conflict between the printed provisions of this Lease and the typewritten or handwritten provisions shall be controlled by the typewritten or handwritten provisions.

45. Offer. Preparation of this Lease by either party or their agent and submission of same to the other Party shall not be deemed an offer to lease to the other Party. This Lease is not intended to be binding until executed and delivered by all Parties hereto.

46. Amendments. This Lease may be modified only in writing, signed by the Parties in interest at the time of the modification. As long as they do not materially change Lessee's obligations hereunder, Lessee agrees to make such reasonable non-monetary modifications to this Lease as may be reasonably required by a Lender in connection with the obtaining of normal financing or refinancing of the Premises.

47. Waiver of Jury Trial. THE PARTIES HEREBY WAIVE THEIR RESPECTIVE RIGHTS TO TRIAL BY JURY IN ANY ACTION OR PROCEEDING INVOLVING THE PROPERTY OR ARISING OUT OF THIS AGREEMENT.

48. Arbitration of Disputes. An Addendum requiring the Arbitration of all disputes between the Parties and/or Brokers arising out of this Lease ☐ is ☑ is not attached to this Lease.

49. Accessibility; Americans with Disabilities Act.

(a) The Premises:

☑ have not undergone an inspection by a Certified Access Specialist (CASp). Note: A Certified Access Specialist (CASp) can inspect the subject premises and determine whether the subject premises comply with all of the applicable construction-related accessibility standards under state law. Although state law does not require a CASp inspection of the subject premises, the commercial property owner or lessor may not prohibit the lessee or tenant from obtaining a CASp inspection of the subject premises for the occupancy or potential occupancy of the lessee or tenant, if requested by the lessee or tenant. The parties shall mutually agree on the arrangements for the time and manner of the CASp inspection, the payment of the fee for the CASp inspection, and the cost of making any repairs necessary to correct violations of construction-related accessibility standards within the premises.

☐ have undergone an inspection by a Certified Access Specialist (CASp) and it was determined that the Premises met all applicable construction-related accessibility standards pursuant to California Civil Code §55.51 et seq. Lessee acknowledges that it received a copy of the inspection report at least 48 hours prior to executing this Lease and agrees to keep such report confidential.

☐ have undergone an inspection by a Certified Access Specialist (CASp) and it was determined that the Premises did not meet all applicable construction-related accessibility standards pursuant to California Civil Code §55.51 et seq. Lessee acknowledges that it received a copy of the inspection report at least 48 hours prior to executing this Lease and agrees to keep such report confidential except as necessary to complete repairs and corrections of violations of construction related accessibility standards.

In the event that the Premises have been issued an inspection report by a CASp the Lessor shall provide a copy of the disability access inspection certificate to Lessee within 7 days of the execution of this Lease.

(b) Since compliance with the Americans with Disabilities Act (ADA) and other state and local accessibility statutes are dependent upon Lessee's specific use of the Premises, Lessor makes no warranty or representation as to whether or not the Premises comply with ADA or any similar legislation. In the event that Lessee's use of the Premises requires modifications or

additions to the Premises in order to be in compliance with ADA or other accessibility statutes, Lessee agrees to make any such necessary modifications and/or additions at Lessee's expense.

LESSOR AND LESSEE HAVE CAREFULLY READ AND REVIEWED THIS LEASE AND EACH TERM AND PROVISION CONTAINED HEREIN, AND BY THE EXECUTION OF THIS LEASE SHOW THEIR INFORMED AND VOLUNTARY CONSENT THERETO. THE PARTIES HEREBY AGREE THAT, AT THE TIME THIS LEASE IS EXECUTED, THE TERMS OF THIS LEASE ARE COMMERCIALLY REASONABLE AND EFFECTUATE THE INTENT AND PURPOSE OF LESSOR AND LESSEE WITH RESPECT TO THE PREMISES.

ATTENTION: NO REPRESENTATION OR RECOMMENDATION IS MADE BY AIR CRE OR BY ANY BROKER AS TO THE LEGAL SUFFICIENCY, LEGAL EFFECT, OR TAX CONSEQUENCES OF THIS LEASE OR THE TRANSACTION TO WHICH IT RELATES. THE PARTIES ARE URGED TO:

1. **SEEK ADVICE OF COUNSEL AS TO THE LEGAL AND TAX CONSEQUENCES OF THIS LEASE.**
2. **RETAIN APPROPRIATE CONSULTANTS TO REVIEW AND INVESTIGATE THE CONDITION OF THE PREMISES. SAID INVESTIGATION SHOULD INCLUDE BUT NOT BE LIMITED TO: THE POSSIBLE PRESENCE OF HAZARDOUS SUBSTANCES, THE ZONING OF THE PREMISES, THE STRUCTURAL INTEGRITY, THE CONDITION OF THE ROOF AND OPERATING SYSTEMS, COMPLIANCE WITH THE AMERICANS WITH DISABILITIES ACT AND THE SUITABILITY OF THE PREMISES FOR LESSEE'S INTENDED USE.**

WARNING: IF THE PREMISES ARE LOCATED IN A STATE OTHER THAN CALIFORNIA, CERTAIN PROVISIONS OF THE LEASE MAY NEED TO BE REVISED TO COMPLY WITH THE LAWS OF THE STATE IN WHICH THE PREMISES ARE LOCATED.

The parties hereto have executed this Lease at the place and on the dates specified above their respective signatures.

Executed at: _____
On: _____

By LESSOR:
SR22 CARLSBAD OAKS DISTRIBUTION, LLC, a California limited liability company

By: _____
Name Printed: Peter S. Robinson
Title: Manager
Phone: (858) 314-3116
Fax: (760) 496-2847
Email: _____

By: _____
Name Printed: _____
Title: _____
Phone: _____
Fax: _____
Email: _____

Address: 111 C Street, Suite 200, Encinitas, CA 92024
Federal ID No.: _____

Executed at: _____
On: _____

By LESSEE:
IONIS PHARMACEUTICALS, INC., a Delaware corporation

By: _____
Name Printed: Elizabeth Hougen
Title: CEO
Phone: _____
Fax: _____
Email: legalnotices@ionisph.com

By: _____
Name Printed: Barbara Mowa
Title: COO
Phone: _____
Fax: _____
Email: _____

Address: 2855 Gazelle Court, Carlsbad, CA 92010
Federal ID No.: _____

APG CARLSBAD I, LLC,
a California limited liability company

By: SMB I GROUP, L.P.,
a Delaware limited partnership
Its: Managing Member

By: K ASSOCIATES,
a California general partnership
Its: General Partner

By: _____
Name: DANIEL FEAN
Its: Managing Member

Ionis Legal MRM

PRE IV C OAKS, LLC,
a California limited liability company

By: PACIFICA REAL ESTATE IV, LLC,
a California limited liability company
Its: Member

By: _____
Steven C. Leonard, Manager

BROKER
Cushman & Wakefield

Attn: Arlo Starck/Dennis Visser
Title: Senior Managing Director/Managing Director

Address: 1000 Aviara Parkway, Suite 100, Carlsbad, CA 92011
Phone: (760) 431-4211
Fax: _____
Email: _____
Federal ID No.: _____
Broker/Agent BRE License #: 01325461/0125595

BROKER
CBRE

Attn: Roger Carlson
Title: Senior Vice President

Address: 5780 Fleet Street, Suite 100
Carlsbad, CA 92008
Phone: (760) 438-8533
Fax: (760) 438-8577
Email: roger.carlson@cbre.com
Federal ID No.: _____
Broker/Agent BRE License #: 01236185

INITIALS

INITIALS

ADDENDUM
TO THAT CERTAIN STANDARD
INDUSTRIAL/COMMERCIAL MULTI-TENANT LEASE-NET
DATED JANUARY 25, 2018, BY AND BETWEEN
SR22 CARLSBAD OAKS DISTRIBUTION, LLC, ETC. ("LESSOR")
AND
IONIS PHARMACEUTICALS, INC. ("LESSEE")

This Addendum amends the provisions of the above-referenced lease including any attached exhibits or addenda thereto (collectively, the "**Lease**"), it being the intent and agreement that the provisions of the Lease are hereby affirmed by the parties, but, to the extent that the provisions of this Addendum conflict with or differ from the terms of the Lease, the provisions of this Addendum shall control. Capitalized terms not defined herein shall have the definitions that are given to such terms in the Lease.

50. Base Rent. During the Original Term, the monthly Base Rent shall be as follows:

Months:	Monthly Base Rent:
Months 1 through 12	$20,196.00
Months 13 through 24	$20,801.88
Months 25 through 36	$21,425.94
Months 37 through 48	$22,068.71
Months 49 through 60	$22,730.78
Months 61 through 63	$23,412.70

51. Abatement of Rent.

(a) For so long as Lessee is not in Breach under the terms of this Lease, the Base Rent payable by Lessee as scheduled in Paragraph 50 above shall be fully abated for months two (2) through four (4) of the Original Term, for a total of three months. Lessee shall continue to pay Lessee's Share of Common Area Operating Expenses during such abatement period.

(b) The abatements set forth in this Paragraph 51 shall be considered an Inducement Provision subject to the provisions of Paragraph 13.3 of this Lease.

52. Condition of Premises. Lessor shall deliver the Premises to Lessee on the Commencement Date in its "AS IS" condition with the existing interior improvements in place, subject to the warranties set forth in Paragraph 2 of the Lease, and Lessor shall not be responsible to construct any additional improvements.

53. [Intentionally Omitted.]

54. Operating Expenses. Lessor estimates that the Lessee's Share of Common Area Operating Expenses will initially be $4,677.50 per month. Lessee understands that this is an estimate only and the actual amount may vary from the estimate.

55. Audit Rights. Lessee shall have the right, at its expense, and upon written notice given to Lessor no later than ninety (90) days after Lessee's receipt of any statement of actual Operating Expenses as provided in Paragraph 4.2(d) of the Lease (the "Reconciliation") to make an audit of all of Lessor's bills, records, receipts, insurance certificates and policies relating to Operating Expenses for the preceding calendar year. Within fifteen (15) business days of Lessor's receipt of such written request of Lessee, Lessor shall make available to Lessee, during normal business hours, at the location where Lessor's books and records are kept, such information as Lessee shall reasonably request. Lessor shall cooperate with Lessee in its explanation of its bills and records. Lessee, at Lessee's sole cost and expense, reserves the right to retain the services of an independent certified public accountant for such audit provided that such accountant is not retained by Lessee on a contingency fee basis. Lessee shall diligently complete any such audit of Operating Expenses and shall deliver to Lessor the written results of such audit within fifteen (15) business days after Lessee receives the same. If Lessor disagrees with the results of Lessee's audit, Lessor and Lessee shall meet and attempt, in good faith, to resolve the dispute. If Lessor and Lessee are unable to

resolve the dispute within thirty (30) days after Lessor's receipt of Lessee's audit, then Lessee shall have the right to submit the dispute to arbitration; this right shall be exercised, if at all, by delivering a written notice of election to arbitrate to Lessor not later than 180 days after receipt of the Reconciliation. Lessor and Lessee shall agree, within 15 days after Lessee's delivery of the arbitration election, to retain an arbitrator, who shall be a mutually acceptable independent certified public accountant with experience in operating expenses for commercial/industrial buildings, who shall make a determination as to the correct amount of Lessee's share of Operating Expenses. The decision shall be delivered simultaneously to Lessor and Lessee and shall be final and binding on Lessor and Lessee. If the arbitrator determines that the amount of the Operating Expenses billed to the Lessee was incorrect, the appropriate party shall pay to the other party the deficiency or overpayment, as applicable, within thirty (30) days following delivery of the arbitrator's decision, without interest. All costs and expenses of the arbitration shall be paid by Lessee unless the final determination in the arbitration is that Lessor overstated Operating Expenses by more than five percent (5%) of the originally reported Operating Expenses, in which case Lessor shall pay all such costs and expenses of the arbitration. Lessee and its auditor shall keep all of Lessor's records strictly confidential and shall not disclose any information gained from its review of Lessor's records to any third party, except as required by law.

56. Signage. Lessee, with the approval of Lessor (which approval shall not be unreasonably withheld) pursuant to the Lessor's sign criteria and the City of Carlsbad, shall be allowed to install exterior identity signage, the exact location and size of any signs to be approved by Lessor, which approval shall not be unreasonably withheld or delayed. Lessee shall be responsible to construct, install and maintain such signage at its sole cost, and shall remove such signage upon expiration or earlier termination of the Lease and repair any damage caused by such removal.

57. Security System. Lessee shall have the right to install a security system for the perimeter and interior of the Premises. Lessee shall be responsible to construct, install and maintain such security system at its sole cost, and shall remove such security system upon expiration or earlier termination of the Lease and repair any damage caused by such removal.

58. Payment to Brokers. Lessor shall pay to the Brokers for the brokerage services rendered by the Brokers in connection with the Lease an amount pursuant to the terms of a separate agreement. Such amounts shall be paid fifty percent (50%) upon full execution of this Lease and fifty percent (50%) on the Commencement Date.

59. Lessee Access. Lessee shall have access to the Premises and use of Lessee's parking spaces seven days a week, 24 hours per day, subject to any reasonable Rules and Regulations established by Lessor.

60. Notices to Lessee. A copy of all notices to Lessee shall be concurrently sent via electronic mail to: legalnotices@ionisph.com.

[Signatures are on next page.]

IN WITNESS THEREOF, Lessor and Lessee have executed this Addendum concurrently with the Lease of even date herewith.

LESSOR:

SR22 CARLSBAD OAKS DISTRIBUTION , LLC,
a California limited liability company

By: _____
Adam S. Robinson, Manager

APG CARLSBAD I, LLC,
a California limited liability company

By: **SMB I GROUP, L.P.,**
a Delaware limited partnership
Its: Managing Member

By: **K ASSOCIATES,**
a California general partnership
Its: General Partner

By: _____
Name: BONNIE CHAN
Its: Managing Member

PRE IV C OAKS, LLC,
a California limited liability company

By: **PACIFICA REAL ESTATE IV, LLC,**
A California limited liability company
Its: Member

By: _____
Steven C. Leonard, Manager

LESSEE:

IONIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: _____
Name: Elizabeth Hougen
Title: CAO

By: _____
Name: Brett Monia
Title: COO

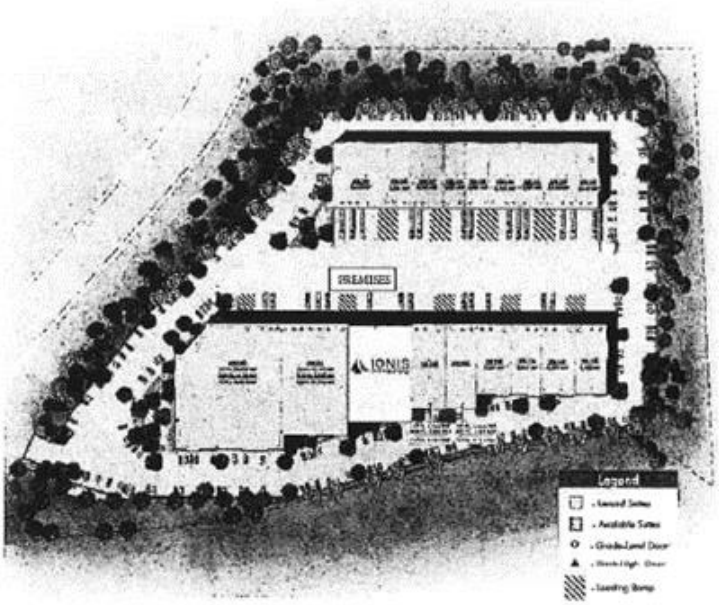
Ionis Legal
mmy

Initials

EH BM
Initials

EXHIBIT A - SITE PLAN

el·e·vate



AIRCRE

OPTION(S) TO EXTEND
STANDARD LEASE ADDENDUM

Dated: January 25, 2018
By and Between
Lessor: 6935 CARLSBAD OAKS DISTRIBUTION, LLC, a California limited liability company; APG CARLSBAD 7, LLC, a California limited liability company; and PRF IV C OAKS, LLC, a California limited liability company
Lessee: IONIS PHARMACEUTICALS, INC., a Delaware corporation
Property Address: 2870 Whiptail Loop, Suite 102, Carlsbad, CA 92010
(street address, city, state, zip)

Paragraph: 61

A. OPTION(S) TO EXTEND:
Lessor hereby grants to Lessee the option to extend the term of this Lease for one (1) additional sixty (60) month period(s) commencing when the prior term expires upon each and all of the following terms and conditions:

(i) In order to exercise an option to extend, Lessee must give written notice of such election to Lessor and Lessor must receive the same at least 9 but not more than 12 months prior to the date that the option period would commence, time being of the essence. If proper notification of the exercise of an option is not given and/or received, such option shall automatically expire. Options (if there are more than one) may only be exercised consecutively.

(ii) The provisions of paragraph 39, including those relating to Lessee's Default set forth in paragraph 39.4 of this Lease, are conditions of this Option.

(iii) Except for the provisions of this Lease granting an option or options to extend the term, all of the terms and conditions of this Lease except where specifically modified by this option shall apply.

(iv) This Option is personal to the original Lessee, and cannot be assigned or exercised by anyone other than said original Lessee and only while the original Lessee is in full possession of the Premises and without the intention of thereafter assigning or subletting.

(v) The monthly rent for each month of the option period shall be calculated as follows, using the method(s) indicated below:

(Check Method(s) to be Used and Fill In Appropriately)

☐ ~~I. Cost of Living Adjustment(s) (COLA)~~

~~a. On (Fill in COLA Date(s)): _____ the Base Rent shall be adjusted by the change, if any, from the Base Month specified below, in the Consumer Price Index of the Bureau of Labor Statistics of the U.S. Department of Labor for (select one): ☐ CPI-W (Urban Wage Earners and Clerical Workers) or ☐ CPI-U (All Urban Consumers), for (Fill in Urban Area): _____. All Items (1982-1984 = 100), herein referred to as "CPI".~~

~~b. The monthly Base Rent payable in accordance with paragraph A.1.a. of this Addendum shall be calculated as follows: the Base Rent set forth in paragraph 1.5 of the attached Lease, shall be multiplied by a fraction the numerator of which shall be the CPI of the calendar month 2 months prior to the month(s) specified in paragraph A.1.a. above during which the adjustment is to take effect, and the denominator of which shall be the CPI of the calendar month which is 2 months prior to (select one): ☐ the first month of the term of this Lease as set forth in paragraph 1.3 ("Base Month") or ☐ (Fill in Other "Base Month"): _____. The sum so calculated shall constitute the new monthly Base Rent hereunder, but in no event, shall any such new monthly Base Rent be less than the Base Rent payable for the month immediately preceding the rent adjustment.~~

~~c. In the event the compilation and/or publication of the CPI shall be transferred to any other governmental department or bureau or agency or shall be discontinued, then the index most nearly the same as the CPI shall be used to make such calculation. In the event that the Parties cannot agree on such alternative index, then the matter shall be submitted for decision to the American Arbitration Association in accordance with the then rules of said Association and the decision of the arbitrators shall be binding upon the parties. The cost of said Arbitration shall be paid equally by the Parties.~~

☑ II. **Market Rental Value Adjustment(s) (MRV)**

a. On (Fill in MRV Adjustment Date(s)) the date on which the option period commences the Base Rent shall be adjusted to the lesser of (a) the Base Rent for the month immediately preceding the option period, or (b) "Market Rental Value" of the property as follows:

1) Four months prior to each Market Rental Value Adjustment Date described above, the Parties shall attempt to agree upon what the new MRV will be on the adjustment date. If agreement cannot be reached, within thirty days, then:

(a) Lessor and Lessee shall immediately appoint a mutually acceptable appraiser or broker to establish the new MRV within the next 30 days. Any associated costs will be split equally between the Parties, or

(b) Both Lessor and Lessee shall each immediately make a reasonable determination of the MRV and submit such determination, in writing, to arbitration in accordance with the following provisions:

(i) Within 15 days thereafter, Lessor and Lessee shall each select an independent third party ☐ appraiser or ☑ broker ("Consultant" - check one) of their choice to act as an arbitrator (Note: the parties may not select either of the Brokers that was involved in negotiating the Lease). The two arbitrators so appointed shall immediately select a third mutually acceptable

Consultant to act as a third arbitrator.

(ii) The 3 arbitrators shall within 30 days of the appointment of the third arbitrator reach a decision as to what the actual MRV for the Premises is, and whether Lessor's or Lessee's submitted MRV is the closest thereto. The decision of a majority of the arbitrators shall be binding on the Parties. The submitted MRV which is determined to be the closest to the actual MRV shall thereafter be used by the Parties.

(iii) If either of the Parties fails to appoint an arbitrator within the specified 15 days, the arbitrator timely appointed by one of them shall reach a decision on his or her own, and said decision shall be binding on the Parties.

(iv) The entire cost of such arbitration shall be paid by the party whose submitted MRV is not selected, ie. the one that is NOT the closest to the actual MRV.

2) When determining MRV, the Lessor, Lessee and Consultants shall consider the terms of comparable market transactions which shall include, but not limited to, rent, rental adjustments, abated rent, lease term and financial condition of tenants.

3) Notwithstanding the foregoing, the new Base Rent shall not be less than the rent payable for the month immediately preceding the rent adjustment.

b. Upon the establishment of each New Market Rental Value:

1) the new MRV will become the new "Base Rent" for the purpose of calculating any further Adjustments, and

2) the first month of each Market Rental Value term shall become the new "Base Month" for the purpose of calculating any further Adjustments.

3) the Base Rent shall increase by three percent (3%) on each anniversary of the MRV Adjustment Date during the remainder of the option period.

☐ III. ~~Fixed Rental Adjustment(s) (FRA)~~

~~The Base Rent shall be increased to the following amounts on the dates set forth below:~~

~~On (Fill in FRA Adjustment Date(s)):~~	~~The New Base Rent shall be:~~
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

☐ ~~IV. Initial Term Adjustments~~

~~The formula used to calculate adjustments to the Base Rate during the original Term of the Lease shall continue to be used during the extended term.~~

~~B. NOTICE:~~

~~Unless specified otherwise herein, notice of any rental adjustments, other than Fixed Rental Adjustments, shall be made as specified in paragraph 23 of the Lease.~~

~~C. BROKER'S FEE:~~

~~The Brokers shall be paid a Brokerage Fee for each adjustment specified above in accordance with paragraph 15 of the Lease or, if applicable, paragraph 9 of the Sublease.~~

Exhibit B – Subleased Premises

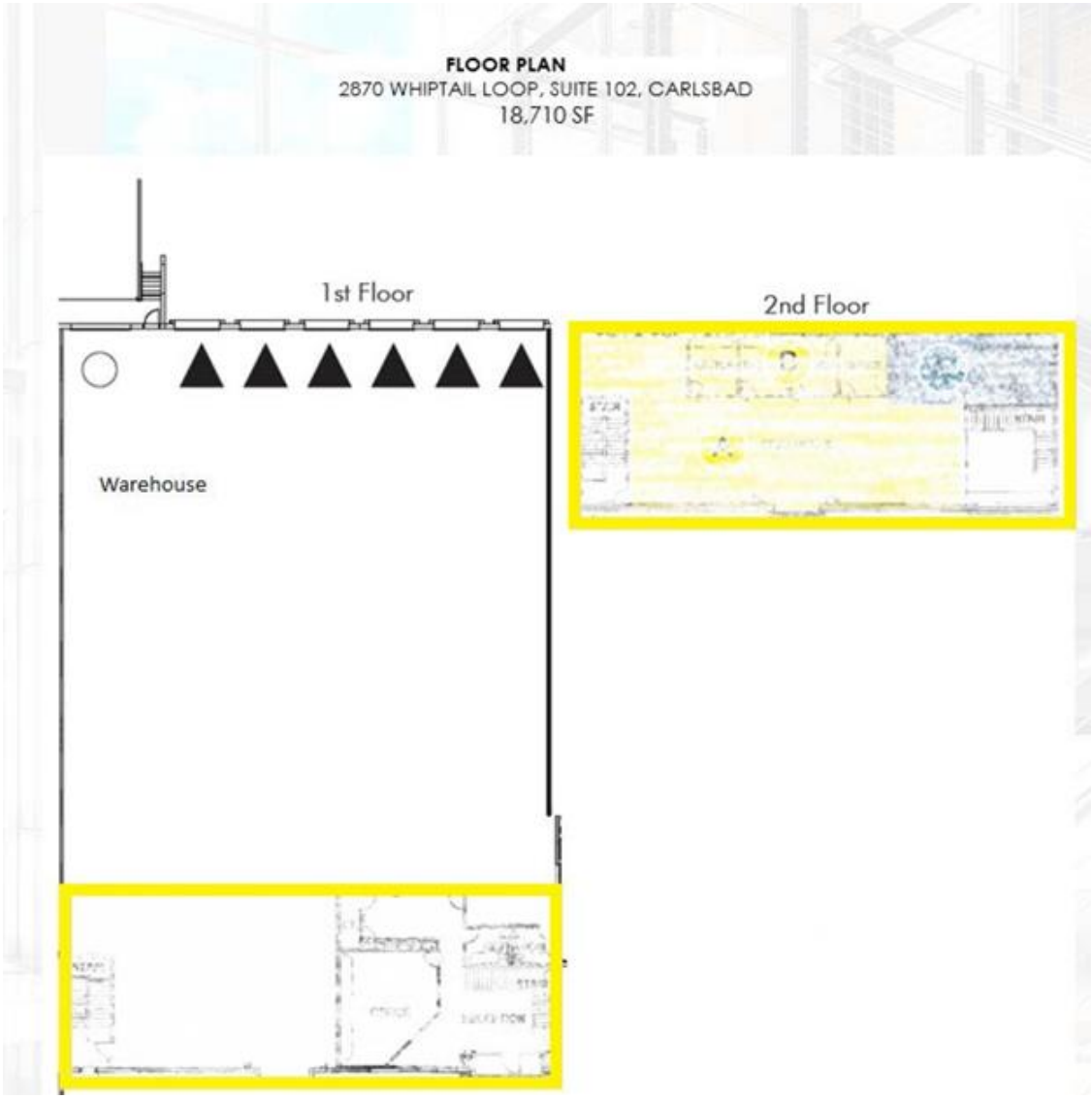


Exhibit C – Rent Schedule

Ionis Pharmaceuticals, Inc.

2870 Whiptail Loop Building Lease

Operating Lease

Debit/ (Credit)

	Date	Rent Payments	CAM CHARGES	TOTAL RENT AND CAM CHARGES	2870 Whiptail Loop Building Lease SCHEDULED RENT & CAM PAYMENTS	
					IONIS	AKCEA
					75%	25%
Beg Bal.						
17 days	March-18	-			-	-
1	April-18	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
2	May-18	-			-	-
3	June-18	-			-	-
4	July-18	-			-	-
5	August-18	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
6	September-18	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
7	October-18	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
8	November-18	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
9	December-18	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
10	January-19	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
11	February-19	20,196.00	4,677.50	24,873.50	18,655.13	6,218.38
12	March-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
13	April-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
14	May-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
15	June-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
16	July-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
17	August-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
18	September-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
19	October-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
20	November-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
21	December-19	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
22	January-20	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
23	February-20	20,801.88	4,677.50	25,479.38	19,109.54	6,369.85
24	March-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
25	April-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
26	May-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
27	June-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
28	July-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
29	August-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
30	September-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
31	October-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
32	November-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
33	December-20	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
34	January-21	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
35	February-21	21,425.94	4,677.50	26,103.44	19,577.58	6,525.86
36	March-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
37	April-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
38	May-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
39	June-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
40	July-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
41	August-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
42	September-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
43	October-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
44	November-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
45	December-21	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
46	January-22	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
47	February-22	22,068.71	4,677.50	26,746.21	20,059.66	6,686.55
48	March-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
49	April-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
50	May-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
51	June-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
52	July-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
53	August-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
54	September-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
55	October-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
56	November-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
57	December-22	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
58	January-23	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
59	February-23	22,730.78	4,677.50	27,408.28	20,556.21	6,852.07
60	March-23	23,412.70	4,677.50	28,090.20	21,067.65	7,022.55
61	April-23	23,412.70	4,677.50	28,090.20	21,067.65	7,022.55
62	May-23	23,412.70	4,677.50	28,090.20	21,067.65	7,022.55
63	June-23	23,412.70	4,677.50	28,090.20	21,067.65	7,022.55
					1,185,147.39	395,049.13
TOTAL LEASE PAYMENTS		1,299,546.52				1,580,196.52
TOTAL LEASE AND CAM PAYMENTS				1,580,196.52		

MONTHLY BILLS

VENDOR	DESCRIPTION	MONTHLY ESTIMATED AMOUNT	
AMAZON	CONFERENCE ROOM ELETRONICS		VARIOUS
SAN DIEGO GAS & ELECTRIC	UTILITIES		VARIOUS
COVERALL OF SAN DIEGO	COMMERCIAL CLEANING OF FLOORS	$556.00	
SIGNA SOLUTIONS, INC.	3 - MONTH MAINTENANCE CONTRACT FOR COPIER	$795.97	
DE LAGE LANDEN FINANCIAL SERVICES, INC.	CANON COPIER		VARIOUS

Exhibit 10.12

Akcea Therapeutics, Inc.
55 Cambridge Parkway, Suite 100
Cambridge, MA 02142

MEMORANDUM

Date: March 9, 2018
To: Akcea Board of Directors
From: Paula Soteropoulos, President & CEO
Subject: Board of Director Compensation

Akcea values the contributions made by its Board of directors. In recognition of these valuable contributions, Akcea will provide each non-employee Director[1] with the compensation described in this memo.

Cash Compensation

Each non-employee Director will receive cash compensation based on his/her role on the Board and Board committees:

Role	Cash Compensation
Board Member (Base retainer)	$40,000
Chairman of the Board (Additional)	$25,000
Committee Chairs (Additional) -Audit -Compensation -Nominating & Gov.	 $18,000 $12,500 $8,000
Committee Member (Additional) -Audit -Compensation -Nominating & Gov.	 $9,000 $6,000 $4,500

Equity Compensation

Each non-employee Director will receive an initial stock option award upon joining the Board, and will receive an annual stock option award for each year of continued service, as follows:

Stock Option Award	No. of Shares
Initial Stock Option Equity Grant	53,000
Annual Stock Option Equity Grant	26,400

The exercise price of each option will be the fair market value of Akcea's common stock on the date of grant.

The options will vest over a four-year period in equal annual installments and be subject to the terms of Akcea's 2015 Equity Incentive Plan. The vesting of the options will accelerate in the case of a change of control of Akcea, as further described your option agreement and the 2015 Equity Incentive Plan.

Akcea reserves the right to amend this compensation policy at any time

[1] Employees of Ionis who serve on the Akcea Board are not eligible for compensation as Akcea Board members.

Exhibit 21.1

LIST OF SUBSIDIARIES

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company
Akcea Therapeutics Canada, Inc., a Canadian Corporation
Akcea Therapeutics France SAS, a French Company
Akcea Therapeutics Germany GmbH, a German Corporation
Akcea Therapeutics Securities Corporation, a Massachusetts Corporation
Akcea Therapeutics Ireland Limited

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration statement (Form S-3ASR No. 333-227403) pertaining to Akcea Therapeutics, Inc.'s shelf registration statement for common stock, preferred stock, debt securities, warrants or any combination of the foregoing;
(2) Registration Statement (Form S-8 No. 333-228969) pertaining to the 2015 Equity Incentive Plan of Akcea Therapeutics, Inc.,
(3) Registration Statement (Form S-8 No. 333-225730) pertaining to the 2015 Equity Incentive Plan and 2017 Employee Stock Purchase Plan of Akcea Therapeutics, Inc., and
(4) Registration Statement (Form S-8 No. 333-219290) pertaining to the 2015 Equity Incentive Plan and 2017 Employee Stock Purchase Plan of Akcea Therapeutics, Inc;

of our report dated March 1, 2019 with respect to the consolidated financial statements of Akcea Therapeutics, Inc., included in this Annual Report (Form 10-K) of Akcea Therapeutics, Inc. for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 1, 2019

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Paula Soteropoulos, certify that:

1. I have reviewed this Annual Report on Form 10-K of Akcea 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(s) 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(s) 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.

Dated: March 1, 2019

By: /s/ Paula Soteropoulos
Paula Soteropoulos
Chief Executive Officer

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Michael MacLean, certify that:

1. I have reviewed this Annual Report on Form 10-K of Akcea 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(s) 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(s) 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.

Dated: March 1, 2019

By: /s/ Michael MacLean
Michael MacLean
Chief 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

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Paula Soteropoulos, the Chief Executive Officer of Akcea Therapeutics, Inc., (the "Company"), and Michael MacLean, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

(1) The Company's Annual Report on Form 10-K for the period ended December 31, 2018, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 1, 2019

By: /s/ Paula Soteropoulos
Paula Soteropoulos
Chief Executive Officer

By: /s/ Michael MacLean
Michael MacLean
Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Akcea Therapeutics, Inc. and will be retained by Akcea Therapeutics, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.