

**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, 2019
- 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 001-37722

**AEGLEA BIOTHERAPEUTICS, INC.**

(Exact name of Registrant as specified in its charter)

**Delaware**  
(State or Other Jurisdiction of  
Incorporation or Organization)

**46-4312787**  
(I.R.S. Employer  
Identification No.)

**805 Las Cimas Parkway  
Suite 100  
Austin, TX**  
(Address of Principal Executive Offices)

**78746**  
(Zip Code)

Registrant's Telephone Number, including area code: (512) 942-2935

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, \$0.0001 Par Value Per Share	AGLE	The Nasdaq Stock Market LLC (Nasdaq Global Market)

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

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

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Exchange 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 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 12b-2 of the Exchange Act). Yes  No

The aggregate market value of the voting stock held by non-affiliates of the Registrant on June 30, 2019 (the last business day of the Registrant's second fiscal quarter), based upon the closing price of \$6.85 of the Registrant's common stock as reported on The Nasdaq Global Market, was approximately \$177.7 million.

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.

Class	Outstanding at February 20, 2020
Common stock, \$0.0001 par value per share	29,085,237 shares

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2020 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2019 fiscal year and is incorporated by reference into Part III of this Report.

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## NOTE ABOUT FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and section 27A of the Securities Act of 1933, as amended, or the Securities Act. All statements contained in this Annual Report other than statements of historical fact, including statements regarding our future results of operations and financial position, business strategy, market size, potential growth opportunities, nonclinical and clinical development activities, efficacy and safety profile of our product candidates, potential therapeutic benefits and economic value of our product candidates, use of net proceeds from our public offerings, our ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of nonclinical studies and clinical trials, commercial collaboration with third parties, and the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, are forward-looking statements. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “predict,” “target,” “intend,” “could,” “would,” “should,” “project,” “plan,” “expect,” and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in Item 1A, “Risk Factors” and elsewhere in this Annual Report. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties, and assumptions, the forward-looking events and circumstances discussed in this Annual Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this report to conform these statements to actual results or to changes in our expectations, except as required by law. You should read this Annual Report with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

Unless the context indicates otherwise, as used in this Annual Report, the terms “Aeglea,” “the Company,” “we,” “us,” and “our” refer to Aeglea BioTherapeutics, Inc., a Delaware corporation, and its subsidiaries taken as a whole, unless otherwise noted. “Aeglea” and all product candidate names are our common law trademarks. This Annual Report contains additional trade names, trademarks and service marks of other companies, which are the property of their respective owners. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

## PART I

### ITEM 1. BUSINESS

#### Overview

We are a clinical-stage biotechnology company developing next-generation human enzyme therapeutics as disruptive solutions for rare and other high-burden diseases. We believe our expertise in enzyme medicine, advanced bioengineering technology, and focused approach enables us to identify and pursue opportunities to address important unmet medical needs for patient communities with few options.

We employ a distinctive, replicable platform to fuel our innovative pipeline, which we believe reduces key risks throughout the development process and provides a greater likelihood of clinical success and commercial adoption.

We are driven by the urgent needs of patient communities who have inadequate or no therapeutic options available to address these debilitating diseases. Our purpose-driven and patient focused approach to the selection and development of novel assets into clinical evaluation is guided by defined strategic considerations:

- Clear, urgent unmet medical need
- Rigorous preclinical data and strong scientific rationale
- Mechanistic opportunity to create or enhance enzymatic activity through novel engineering
- Meaningful and sustainable commercial opportunities
- Potential to be first in class or best in class, with limited competition

#### Our Strategy

We continually advance toward our vision to become the preeminent human enzyme company, dedicated to the discovery, development, and commercialization of next generation human enzyme therapeutics that address defined unmet medical needs and transform lives. With a strategic approach, we are:

- ***Pursuing opportunities for novel human enzyme-based therapeutics in areas where regulation of abnormal metabolism may deliver meaningful medical benefits.***

Our focus is on rare and other high-burden diseases where there is a plausible link between disease development, progression, and metabolite levels including amino acids, opening an opportunity for novel engineered enzyme therapeutics. Grounded by our enzyme expertise, we purposefully select programs to advance into clinical development based on strong biological rationale and robust preclinical evidence where potential therapy can transform patient outcomes.

- ***Implementing patient identification strategies to increase the probability of clinical success.***

An integral part of our product development approach is to identify patient populations with the greatest potential to benefit from our metabolism focused approaches. In rare genetic diseases, this strategy is focused on identifying misdiagnosed and undiagnosed patients. For example, in the United States, we are actively pursuing avenues to improve disease state awareness and diagnosis of Arginase 1 Deficiency.

- ***Advancing our lead product candidate, pegzilarginase, through clinical development and into commercialization.***

We believe pegzilarginase is the only therapeutic in clinical development that addresses the underlying drivers of disease progression for the treatment of Arginase 1 Deficiency. Pegzilarginase is currently being evaluated in two ongoing clinical trials for Arginase 1 Deficiency, consisting of the global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial and our open label extension study. The PEACE trial is a single, global pivotal trial with a primary endpoint of plasma arginine reduction and secondary endpoints including clinical outcome assessments focused primarily on mobility, in addition to safety and pharmacokinetics. We expect to complete enrollment in the PEACE trial in the third quarter of 2020 and anticipate that topline data will be available in the first quarter of 2021.

- ***Concurrently developing multiple product candidates with the goal of approval and commercialization in the US and internationally.***

We are building a diversified portfolio with multiple human enzyme therapeutic candidates, with complementary opportunities to evaluate enzyme solutions for patient communities with few options today. With this multi-asset strategy, we are leveraging organizational efficiencies and economies of scale, and are investing in our internal research, development, and commercialization capabilities to continually enrich our portfolio.

In developing programs for diseases with substantial unmet medical need, we seek opportunities with meaningful commercial potential and with limited or no current competition. We retain worldwide intellectual property rights to all our product candidates, and intend to pursue clinical and regulatory programs for approval in the United States and internationally. Over time, we intend to establish a multi-country commercial organization in rare genetic diseases with commercial partnerships in select regions.

## **Our Focus—Enzyme-based Therapeutic Opportunities**

We leverage our enzyme engineering capabilities to focus on developing therapeutics to treat diseases with abnormally high levels of metabolites. Many of these diseases arise due to inborn errors of metabolism. Metabolism refers to fundamental chemical reactions that are critical to life-sustaining processes. Metabolism follows specific pathways that are comprised of various biochemical reactions generally catalyzed by proteins known as enzymes. Enzymes accelerate complex reactions and serve as key regulators of metabolic pathways by responding to changes in the cell's environment or signals from other cells.

An in-depth understanding of abnormal metabolic pathways is crucial to developing therapies that may address various disease states, including rare genetic diseases. Our core capability of exploiting these abnormal metabolic pathways has allowed us to engineer human enzyme therapies with the potential to reduce harmful levels of metabolites, including amino acids that may address important unmet needs in rare genetic diseases.

### ***Understanding Rare Genetic Disease and Arginase 1 Deficiency***

The incidence of a single metabolic abnormality typically occurs in fewer than one per 100,000 live births. While rare, most of these diseases have severe or life-threatening characteristics and many metabolic abnormalities are likely to be under-diagnosed. Current treatment options for these disorders are limited. While diet modification or nutrient supplementation can provide some benefit to patients, several metabolic abnormalities have been treated successfully with enzyme therapy.

We are targeting Arginase 1 Deficiency with our lead product candidate, pegzilarginase. Arginase 1 Deficiency is a serious progressive disease with significant morbidity and early mortality. This disease is caused by deficiency of a key arginine metabolizing enzyme. This leads to two important harmful metabolic effects: (1) the accumulation of high levels of arginine and other arginine derived metabolites, and (2) an impairment of the urea cycle which leads to elevation of ammonia levels, especially at times of stress. The high plasma arginine level is believed to be the key driver of the spasticity, developmental delays, and seizures that develop in early childhood and progress over time. The impairment of the urea cycle also means that these patients are at risk of episodic and sometimes persistent hyperammonemia, which causes irritability, nausea, and vomiting with potential to progress to brain swelling, encephalopathy, reduced life expectancy, and death.

There are currently no effective treatment options or approved therapeutic agents specifically indicated for Arginase 1 Deficiency that treat the underlying cause of this disease. Current disease management practice includes a medical diet with protein restriction, ammonia scavengers, and adjustments to essential amino acids. Medical literature suggests that disease progression can be slowed with strict adherence to dietary protein restriction, which often includes the use of specially formulated supplements. Such dietary modification has been shown to partially reduce plasma arginine levels, but generally does not consistently reach the range stipulated by medical guidelines. Therefore, this disease management approach is generally inadequate to treat the majority of patients, unpalatable, and difficult to manage. Ammonia-scavenging drugs such as RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylbutyrate) are used to manage elevated ammonia levels. In some cases, liver transplantation has been utilized to treat Arginase 1 Deficiency; however, this intervention is available only to a small fraction of patients and carries significant procedural risk.

The lack of effective treatment options that directly address the cause of Arginase 1 Deficiency supports the need for a therapy that manages the harmful metabolic effects caused by accumulation of high levels of arginine and other arginine-derived metabolites (also referred to as guanidino compounds). The development of an arginine-reducing therapeutic introduced early in a patient's life could potentially minimize the exposure to the neurotoxic effects of elevated arginine, its metabolites, and ammonia, as well as potentially enabling improved protein intake. Reduction and maintenance of plasma arginine levels to within levels recommended by medical guidance for an extended period during the pegzilarginase dosing schedule has the potential to slow or halt the progression of the disease, thereby offering the potential for more normal growth and development in these patients.

Arginase 1 Deficiency is a rare disorder, and disease prevalence has not been well established in the medical literature. Based on a genetic prevalence analysis commissioned by us, we estimate that the Arginase 1 Deficiency population is greater than 2,500 patients in the global addressable markets. The genetic prevalence-based methodology has the ability to account for misdiagnosis of the disease and to address limitations in newborn screening methodology, including naturally low arginine levels in newborns and lack of geographic availability or standardization of testing. Presently, only 34 U.S. states and jurisdictions screen for Arginase 1 Deficiency, and screening in Europe is not universal. Because the symptoms of Arginase 1 Deficiency may overlap with other disorders such as hereditary spastic paraplegia, cerebral palsy or epilepsy, the prevalence of Arginase 1 Deficiency may be underestimated in regions that do not mandate newborn screening for this disease. To date we have identified more than 200 patients in the major addressable markets, primarily in the U.S. and Europe. In the U.S. we have identified more than 100 patients, representing a 40% penetration into the genetic prevalent population.

### ***Understanding Homocystinuria***

Homocystinuria is an inherited disorder of methionine metabolism that results in elevated homocysteine and homocystine, or tHcy, in plasma and urine. This leads to a broad range of serious consequences with irreversible morbidity due to lens dislocation, skeletal abnormality, vascular complication and intellectual dysfunction, as well as reduced life expectancy.

Homocystinuria due to cystathionine  $\beta$ -synthase (CBS) deficiency, also known as classical Homocystinuria, is the most common form of the disease with over 160 genetic mutations identified. These mutations may have different effects on how the CBS enzyme functions which may in turn impact the level of tHcy and the response to treatment. CBS deficient patients who respond to pyridoxine resulting in decreases of methionine and homocysteine are considered B6 responsive, however, many patients are unable to achieve target levels of tHcy through diet and/or pyridoxine alone and thus betaine is recommended as an adjunctive treatment. As a result, some subjects have severe childhood-onset multisystem disease, while others may be asymptomatic into adulthood, likewise the spectrum and severity of disease is also variable.

The natural history of CBS deficiency is understood and documented in the medical literature. While newborn screening is universally implemented in the U.S. (and widely available elsewhere), for technical reasons it only detects a proportion of cases. Patients can present with homocystinuria in childhood with a significant event, such as thrombosis, ocular lens dislocation, severe myopia, skeletal fracture, and/or other manifestations such as developmental delay or cognitive impairment. In adulthood, the most common presentation is with a thrombotic event. Untreated, the disease results in higher mortality, with B6 non-responsive patients having a 23% mortality by the age of 30. Medical literature has reported that outcomes are better in patients with lower tHcy with fewer complications and improved intellectual function. While no long-term prospective data exists, recent guidelines based on expert review recommend a target tHcy of less than 120  $\mu$ M although some physicians aim for even lower targets with a combination approach.

The goal of treatment for Homocystinuria due to CBS deficiency is to maintain consistent plasma tHcy levels as close to normal as possible or, at a minimum, below the currently defined biochemical targets. Current disease management is lifelong and includes dietary protein (methionine) restriction with amino acid replacement either alone or with pyridoxine (vitamin B6), and betaine supplementation, which is generally insufficient to effectively control all but the mildest form of the disease. As is the case with other medical diets, adherence is challenging and nutrient supplementation is often necessary to prevent deficiencies that arise from a lack of normal natural dietary protein intake. Some CBS deficient patients respond to very high doses of pyridoxine (vitamin B6) resulting in decreases of methionine and homocysteine, however, many patients are unable to achieve target levels of tHcy through diet and/or pyridoxine alone and thus betaine is recommended as an adjunctive treatment. Although generally well tolerated, some subjects dislike the taste and/or fishy odor, which may lead to poor compliance. Compliance is also hampered by the large doses required.

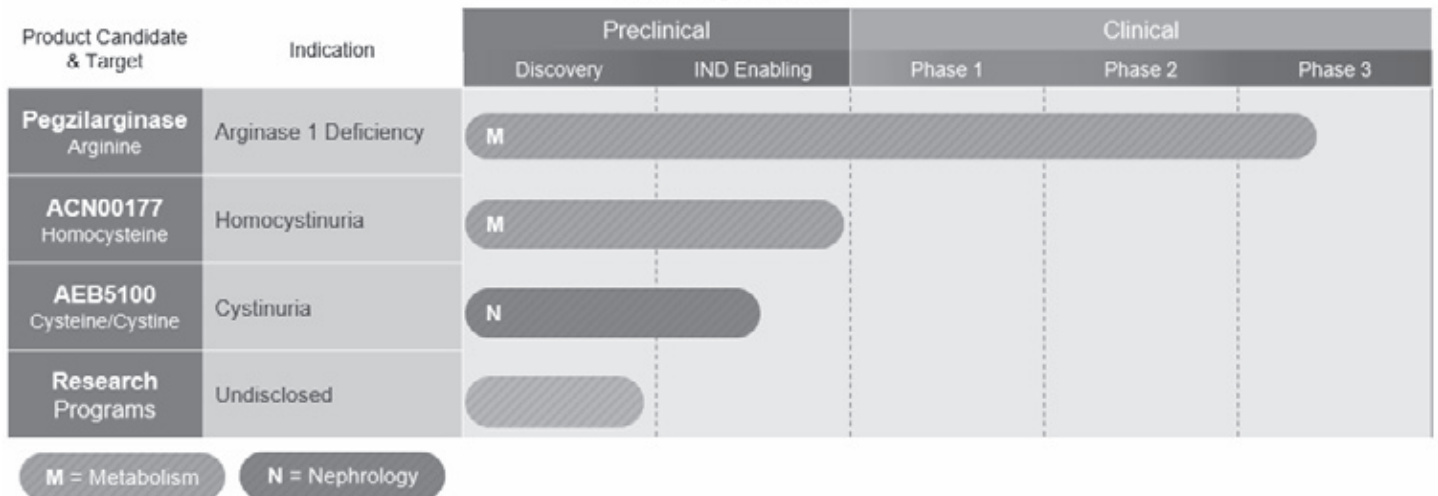
There is a significant unmet need for patients in whom tHcy levels remain high, and the risk of complications persists. In addition, many patients find compliance with diet to be restrictive and cannot maintain tHcy levels within the target range. The lack of effective interventions to directly address the consequences of CBS deficiency support the need for a therapy to reduce the harmful effects of persistently raised tHcy. The introduction of a tHcy reducing therapeutic could ultimately prevent major thrombotic, ocular and skeletal complications, offering the potential to reduce morbidity and mortality in these patients.

The estimated prevalence in the United States is between 1:133,000 to 1:375,000 and the global prevalence varies from 1:1,800 to 1:900,000 depending on the population group. Assuming a less than normal life span, we believe that at least 5,000 individuals in the global addressable markets have B6 non-responsive Homocystinuria due to CBS deficiency.

## Our Development Programs

The following summarizes our most advanced product candidates, each of which is described in further detail below.

### Our Pipeline



### Pegzilarginase in Arginase 1 Deficiency

**Overview:** Our lead product candidate, pegzilarginase, is a recombinant human Arginase 1 that enzymatically degrades the amino acid arginine. We engineered pegzilarginase with modifications that enhance the stability and arginine-degrading activity of the enzyme in human plasma. For Arginase 1 Deficiency, which is a rare progressive disease, we believe pegzilarginase may reduce the harmful metabolic effects caused by the accumulation of high levels of arginine and other arginine-derived metabolites.

**PEACE - Global Pivotal Phase 3 Study of Pegzilarginase in Patients with Arginase 1 Deficiency:** We are currently conducting our Phase 3 PEACE trial to evaluate the safety and efficacy of pegzilarginase. The trial is believed to be the first-ever investigative therapy that directly addresses the high arginine levels that are believed to be the key drivers of this devastating disease for patients with Arginase 1 Deficiency. We designed the PEACE trial based on input from the FDA and EMA. We expect to complete enrollment in the PEACE trial in the third quarter of 2020 and anticipate that topline data from the Phase 3 PEACE study will be available in the first quarter of 2021.

PEACE is a single, global, randomized, double-blind, placebo-controlled trial designed to assess the effects of treatment with pegzilarginase versus placebo over 24 weeks with a primary endpoint of statistically significant plasma arginine reduction from baseline. The primary endpoint assesses the effectiveness of pegzilarginase in lowering plasma arginine levels given the evidence that plasma arginine control has the potential to improve the clinical status and slow disease progression in patients with Arginase 1 Deficiency. Secondary endpoints will include clinical outcome assessments focused primarily on mobility, in addition to safety and pharmacokinetics. The pivotal trial will span approximately 10 countries and 25 to 30 clinical sites. Upon completion of the 24-week treatment period, patients may qualify to participate in a long-term extension study of pegzilarginase. The FDA and EMA indicated that data from this Phase 3 PEACE trial showing plasma arginine reduction in conjunction with improvements in clinically meaningful aspects of the disease may be sufficient to support a marketing application for pegzilarginase in Arginase 1 Deficiency.

We plan to enroll approximately 30 (pediatric and adult) patients with Arginase 1 Deficiency. Patients enrolled in the trial are randomized on a two-to-one basis to receive weekly infusions of pegzilarginase (0.1 mg/kg), or placebo for the double-blind treatment period of 24 weeks. Dose adjustments during this period can be made to optimize plasma arginine control for levels outside the range of 50 to 150  $\mu\text{M}$ .

Patients will be considered eligible for the PEACE trial during screening if they exhibit average plasma arginine levels of greater than 250  $\mu\text{M}$ , are greater than two years of age and have a deficit in at least one dimension of mobility and/or adaptive behavior. All assessments and dose adjustments will be conducted in a blinded fashion at pre-specified intervals. Patients will remain on current disease management for the duration of the Phase 3 PEACE trial.

In addition to the primary endpoint of plasma arginine reduction, secondary endpoints in the Phase 3 PEACE trial will evaluate pegzilarginase relative to placebo through a multi-dimensional assessment of clinical response. A clinical responder is defined as a patient exhibiting improvement from baseline in mobility, measured by a 2 Minute Walk Test or Gross Motor Function Measure D (standing) or E (walking, running, and jumping). Additional secondary endpoints include a response rate for each individual assessment, the total number of mobility and adaptive behavior responses per patient and the proportion of patients with plasma arginine below medical guidance of 200  $\mu\text{M}$ .

*Phase 1/2 Open Label Study of Pegzilarginase in Patients with Arginase 1 Deficiency:* We completed a Phase 1/2 clinical trial for the treatment of patients with Arginase 1 Deficiency to assess the safety and clinical activity of pegzilarginase. The Phase 1/2, multi-center, single-arm, open label trial of pegzilarginase enrolled 16 adult and pediatric patients with Arginase 1 Deficiency in the United States, Canada, and Europe, exceeding the initial target of 10 patients. The Phase 1/2 dosing was completed in February 2019, with 14 patients completing 8 weeks of repeat dosing. The trial investigated both single ascending doses and repeated dosing. The primary endpoint of the trial was safety and tolerability of intravenous administration of pegzilarginase in patients with Arginase 1 Deficiency. The trial also evaluated the pharmacokinetic and pharmacodynamic effects of repeated doses of pegzilarginase on plasma arginine levels. Additionally, patients who completed the repeat dose part of the Phase 1/2 trial were eligible to enroll in a long-term open label extension study, with 14 out of 14 patients that completed the Phase 1/2 trial enrolling into the extension study.

*Phase 2 Open Label Extension Study to Evaluate the Long-Term Safety, Tolerability and Effects of Pegzilarginase in Patients with Arginase 1 Deficiency Who Received Treatment in a Previous Study:* After completing the repeat dose portion of the Phase 1/2 study and at least four weeks of post-treatment observation, patients were allowed to continue treatment with pegzilarginase by enrolling in a long-term open label extension study. This study is expected to provide important insights into the longer-term clinical effects of reducing plasma arginine.

In September 2019, we announced 20-dose data on 14 patients from our completed Phase 1/2 trial and ongoing Phase 2 open-label extension trial for pegzilarginase in patients with Arginase 1 Deficiency. We reported all patients continued to demonstrate marked and sustained reductions in plasma arginine following 20 doses of pegzilarginase and 79% (11 of 14) of patients were clinical responders, using mobility assessment components that correspond with the pivotal PEACE trial secondary endpoints. Pegzilarginase was well tolerated and the rates of treatment-related adverse events decreased over time. Serious adverse events included hypersensitivity and hyperammonemia, which were infrequent, expected, and managed with standard treatment and did not lead to any patient discontinuations.

Additionally, we announced in September 2019 that 10 of the 14 patients from our ongoing Phase 2 open-label extension trial for pegzilarginase in patients with Arginase 1 Deficiency had been dosed subcutaneously, or sc, with pegzilarginase. Administration of pegzilarginase by the subcutaneous route was shown to control plasma arginine levels and was generally well tolerated, with only four mild injection site reactions related to pegzilarginase in more than 200 injections. All 10 eligible patients switched to, and remained on, pegzilarginase (sc), with no patient discontinuations through the announcement date. We are evaluating the pegzilarginase (sc) route of administration in our Phase 2 open-label extension trial and will review data to determine the best path for selecting the preferred route of administration for our BLA submission.

*Regulatory Designations:* We have obtained Orphan Drug Designation from the FDA and EMA, as well as Fast Track and Breakthrough Therapy Designations from the FDA, for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. In addition, the FDA granted a Rare Pediatric Disease designation for pegzilarginase for the treatment of Arginase 1 Deficiency. This designation by the FDA confirms our eligibility to receive a Rare Pediatric Disease priority review voucher upon approval of a qualifying biologics license application for pegzilarginase if completed before October 1, 2022.

We met with the FDA in October 2019 to discuss the regulatory approval pathway for pegzilarginase, in a previously scheduled meeting before receiving Breakthrough Therapy Designation. The meeting provided greater clarity over several requirements to support approval through completion of the Phase 3 PEACE trial, including plans for the CMC portion of our BLA submission, immunogenicity assessments, and aggregation of the safety database. We expect to continue additional interactions with the FDA post-Breakthrough Therapy Designation.



## **ACN00177 in Homocystinuria**

*Overview:* Our product candidate, ACN00177, is a novel PEGylated, or polyethylene glycol modified, human enzyme engineered to degrade free homocysteine and homocystine. We engineered ACN00177 by directed mutagenesis of amino acid residues within the active site of human cystathionine  $\gamma$ -lyase, resulting in a molecule that has high substrate specificity for homocysteine and homocystine but not for the native substrate, cystathionine. For classical Homocystinuria patients, we believe ACN00177 may ameliorate the adverse impact of CBS enzyme deficiency in the transsulfuration pathway by providing an alternate pathway for enzymatic degradation of high plasma total homocysteine levels.

*Phase 1/2 Open Label Study of ACN00177 in Patients with Homocystinuria:* We expect to initiate a Phase 1/2 clinical trial for the treatment of patients with Homocystinuria in the second quarter of 2020 and expect initial data in the first quarter of 2021. The primary objective of the trial is to evaluate the safety and tolerability of ACN00177 in subjects with Homocystinuria due to CBS deficiency. As a secondary objective, the trial will also characterize the pharmacokinetics and pharmacodynamics relationship of ACN00177 after single and multiple doses following intravenous and subcutaneous administration, as well as the magnitude of change in plasma tHcy. In January 2020, we announced the submission of a Clinical Trial Application with the United Kingdom's Medicines and Healthcare Products Regulatory Agency, or MHRA, for ACN00177.

## **Pegzilarginase in Cancer**

*Phase 1/2 Combination Trial in Patients with SCLC:* We concluded enrollment in an open label Phase 2 clinical collaboration with Merck to evaluate the combination of pegzilarginase with Merck's anti-PD1 therapy, KEYTRUDA® (pembrolizumab) for the treatment of patients with small cell lung cancer, or SCLC, that relapsed or progressed after platinum-based chemotherapy. The Phase 2 primary objective is objective response rate, and secondary objectives include safety, clinical benefit rate, time to response, duration of response, progression free survival, and overall survival.

In August 2019, we announced interim data from 35 patients in this Phase 1/2 combination clinical trial. As of October 31, 2019, the clinical trial had resulted in one complete response, six partial responses, and nine patients with stable disease. This combination was generally well tolerated and safety observations were consistent with prior studies of pegzilarginase in patients with cancer. We intend to submit the results for presentation or publication after the final dataset becomes available. We are currently exploring partnership opportunities for further development.

*Phase 1 Dose Escalation Trial of Pegzilarginase in Patients with Advanced Solid Tumors:* We completed a Phase 1 open label, multiple dose, dose escalation clinical trial in patients with advanced solid tumors. The primary objective of dose-escalation was to determine the maximum tolerated dose, and secondary objectives were to evaluate the safety, tolerability, and pharmacokinetic profile of pegzilarginase. The inclusion criteria included patients with locally advanced or metastatic solid tumors that failed to respond to or progressed under standard treatment, could not tolerate standard therapies, or for which no standard therapy exists.

Upon completion of the dose escalation in patients with advanced solid tumors, we initiated three separate cohort expansions of patients with SCLC, uveal melanoma, and cutaneous melanoma. These cancer types were selected because nonclinical studies and the medical literature suggest that a significant fraction of patients are expected to have cancers that are dependent on extracellular arginine. The primary endpoint of each cohort expansion was to assess the safety of pegzilarginase in patients with each tumor type. Secondary endpoints included the assessment of pharmacokinetics, pharmacodynamics and clinical response.

In March 2019, we announced the completion of enrollment of three separate cohort expansions of patients with heavily pre-treated SCLC, uveal melanoma, and cutaneous melanoma. We previously presented interim clinical data at the European Society for Medical Oncology 2018 Congress in October 2018, demonstrating that pegzilarginase monotherapy resulted in anti-tumor activity in heavily pre-treated patients with advanced uveal and cutaneous melanoma. Across the two advanced melanoma cohorts, 28 patients were enrolled with one confirmed partial response observed and eight patients with stable disease at 8 weeks. Three patients experienced treatment-related, Grade 3 serious adverse events, including asthenia and failure to thrive, vomiting and dehydration. For the SCLC cohort, no objective responses and no new safety findings were observed in the 13 heavily-pretreated patients in the single agent expansion arm, which completed enrollment in December 2018. Anti-tumor activity appeared greater in melanomas lacking argininosuccinate synthetase 1 (ASS1) expression, which is consistent with preclinical studies that suggest tumors lacking ASS1 expression are dependent on extracellular arginine for survival. Additionally, pegzilarginase was shown to rapidly and sustainably deplete plasma arginine. We are currently exploring partnership opportunities for further development.

## **Preclinical Pipeline**

### ***AEB5100 Program in Cystinuria***

Cystinuria is a rare genetic disease characterized by frequent and recurrent kidney stone formation requiring multiple procedural interventions, and by an increased risk of chronic kidney disease. Cystinuria occurs due to genetic mutations in amino acid transporters that lead to increased amounts of cystine in the urine. This results in high cystine concentrations in the urine and formation of kidney stones. As such, we engineered our AEB5100 program candidate to reduce plasma cystine and cysteine levels with accompanying reductions in urine cystine concentrations as an approach to inhibit both cystine crystal and kidney stone formation. We estimate there are greater than 10,000 individuals in the global addressable market with cystinuria.

In October 2018, we presented data on an early lead molecule from our AEB5100 program demonstrating reductions in plasma and urine cystine levels, accompanied by reduced kidney stone formation in a preclinical model of cystinuria. We are pursuing investigational new drug (IND)-enabling studies for an improved lead molecule from the AEB5100 program and expect to provide dose response and bioavailability data in the second quarter of 2020 and submit an IND or CTA for this program in the second half of 2020.

## **Research Programs**

A significant number of metabolic diseases remain without an effective treatment. Our in-house team of scientists and clinicians assess whether human enzymes are available to decrease the potential disease promoting metabolites in diseases with unmet medical need. If a human enzyme is not available, our team of protein engineers will introduce changes into alternative human enzyme scaffolds to alter their specificity for the proposed disease-causing metabolite. The generation of lead molecules using this approach enables us to investigate the preclinical impact of these molecules in animal models of the disease, and with supporting positive data, additional engineering may be performed to ensure the clinical candidate meets manufacturing requirements and has characteristics that are compatible with the patient needs.

## **Intellectual Property**

Our success depends in part on our ability to obtain and maintain patents and other forms of intellectual property rights, including in-licenses of intellectual property rights of others, for our product candidates, methods used to manufacture our product candidates and methods for treating patients using our product candidates, as well as our ability to preserve our trade secrets, to prevent third parties from infringing upon our proprietary rights and to operate without infringing upon the proprietary rights of others.

We own three granted US Patents directed towards compositions of pegzilarginase as well as to various mutations in the arginase 1 amino acid sequence. These patents will expire in 2029 in the absence of any patent term extension. There are also granted patents directed towards the composition of pegzilarginase in Europe and Japan, as well as pending patent applications in the US, Europe and Canada. We also own a pending US application and a pending PCT application directed towards the use of pegzilarginase in the treatment of arginase 1 deficiency. Any patents that issue from these US or PCT applications will expire in 2038 absent any patent term adjustment or patent term extension. We further own a pending US application and pending foreign counterpart applications directed towards the use of pegzilarginase in the treatment of cancer, and any patents issued from these applications will expire in 2037 absent any patent term adjustment or patent term extension.

We are the exclusive licensee of a US application and pending foreign counterpart applications directed towards the AEB4104 program which covers recombinant human enzymes that degrade the amino acid homocysteine and homocystine. Any patents that issue from these applications will expire in 2038 absent any patent term adjustment or patent term extension. We also are the exclusive licensee of a US application and foreign counterpart applications directed towards use of a modified cystathionine- $\gamma$ -lyase (CGL) enzyme with activity to degrade plasma cystine and cysteine, and any patents issued from these applications will expire in 2037 absent any patent term adjustment or patent term extension. We also license a PCT patent application directed to the AEB5100 program which covers novel recombinant human enzymes that degrade plasma cystine and cysteine, and any patents that issue from this PCT application will expire in 2039 absent any patent term adjustment or patent term extension. The AEB2109 program covers engineered human enzyme that targets the degradation of the amino acid methionine. We own four granted US patents and pending US and foreign patent applications directed towards the compositions of the AEB2109 program. These patents and any further patents that issue from these applications will expire in 2031, absent any patent term adjustment or patent term extension.

We aim to take advantage of all of the intellectual property rights that are available to us and believe that this comprehensive approach will provide us with proprietary positions for our product candidates, where available.

Patents may extend for varying periods according to the date of patent filing or grant and the legal term of patents in various countries where patent protection is obtained. The actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country.

We also protect our proprietary information by requiring our employees, consultants, contractors and other advisors to execute nondisclosure and assignment of invention agreements upon commencement of their respective employment or engagement. In addition, we also require confidentiality or service agreements from third parties that receive our confidential information or materials.

## **Licensing**

On December 24, 2013, two of our wholly-owned subsidiaries, AECCase, Inc., or AECCase, and AEMase, Inc., or AEMase, entered into license agreements with the University under which the University has granted to AECCase and AEMase exclusive, worldwide, sublicenseable licenses. The University granted to AECCase a license under a patent application relating to the right to use, develop, manufacture, and market technology related to our AEB3103 product candidate. The University granted to AEMase license under a patent relating to the right to use technology related to our AEB2109 product candidate. In January 2017, we entered into an Amended and Restated Patent License Agreement, or the Restated License, with the University which consolidated the two license agreements dated December 24, 2013, revised certain obligations, and licensed additional patent applications to Aeglea. We have also entered into amendments to the Restated License in August 2017, December 2017, and December 2018 to license additional patent applications.

With respect to each product candidate covered by the Restated License, we could be required to pay the University up to \$6.4 million in milestone payments based on the achievement of certain development milestones, including clinical trials and regulatory approvals, the majority of which are due upon the achievement of later development milestones, including a \$5.0 million payment due on regulatory approval of a product and a \$0.5 million payment payable on final regulatory approval of a product for a second indication. In addition, we are required to pay the University a low single digit royalty on worldwide-net sales of products covered under the Restated License, together with a revenue share on non-royalty consideration received from sublicensees. The rate of the revenue share ranges from 6.5% to 25%, depending on the date the sublicense agreement is signed. The term of the Restated License continues until the expiration of the last to expire of the patents licensed thereunder. The University may terminate the agreement under certain circumstances, including for a breach by us that is not cured within 30 or 60 days of notice (depending on the type of breach), or if we or any of our affiliates or sublicensees participate in any proceeding to challenge the licensed patent rights (unless, with respect to sublicensees, we terminate the applicable sublicense). As of December 31, 2019, we have paid \$0.2 million under these license agreements.

## **Grant Agreement**

In June 2015, we entered into a Cancer Research Grant Contract, or the Grant Contract, with the Cancer Prevention and Research Institute of Texas, or CPRIT, under which CPRIT awarded us a grant not to exceed \$19.8 million to be used to develop novel cancer treatments by exploiting the unique metabolism of cancer cells. The contract ended in May 2018 with the full \$19.8 million in grant proceeds collected and recognized as revenue under the Grant Contract.

Pursuant to the Grant Contract, we granted to CPRIT a non-exclusive, irrevocable, royalty-free, perpetual, worldwide license to any technology and intellectual property resulting from the grant-funded activities and any other intellectual property that is owned by us and necessary for the exploitation of the technology and intellectual property resulting from the grant-funded activities, or the Project Results, for and on behalf of CPRIT and other governmental entities and agencies of the State of Texas and private or independent institutions of higher education located in Texas for education, research and other non-commercial purposes only. The terms of the Grant Contract require that we pay tiered royalties in the low- to mid-single digit percentages on revenues from sales and licenses of products or services that are based upon, utilize, are developed from or materially incorporate Project Results. Such royalties reduced to less than one percent after a mid-single-digit multiple of the grant funds have been repaid to CPRIT in royalties. Such royalties are payable for so long as we have marketing exclusivity or patents covering the applicable product or service (or twelve years from first commercial sale of such product or service in certain countries if there is no such exclusivity or patent protection).

If we abandon patent applications or patents covering Project Results in certain major market countries, CPRIT can, at its own cost, take over the prosecution and maintenance of such patents and is granted a non-exclusive, irrevocable, royalty-free, perpetual license with right to sublicense in such country to the applicable Project Results. We are required to use diligent and commercially reasonable efforts to commercialize at least one commercial product or service or otherwise bring to practical application the Project Results. If CPRIT notifies us of our failure with respect to the foregoing, and such failure is not owing to material safety concerns, then, at CPRIT's option, the applicable Project Results would be transferred to CPRIT and CPRIT would be granted a non-exclusive license to any other intellectual property that is owned by us and necessary for the exploitation of the Project Results, and CPRIT, at its own cost, can commercialize products or services that are based upon, utilize, are developed from or materially incorporate Project Results. CPRIT's option is subject to our ability to cure any failures identified by CPRIT within 60 days and a requirement to negotiate in good faith with us with respect to an alternative commercialization strategy for a period of 180 days.

## Competition

While we believe that our expertise in enzyme medicine, advanced bioengineering technology, preclinical development experience, and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, and ultimately biosimilar and generic drug companies. Recent advances in gene-based medicine, such as gene therapy have resulted in market approvals of DNA and RNA-based therapeutics in certain rare genetic diseases. However, no gene therapy drugs have yet to demonstrate clinical success in the type of complex diseases targeted by our research approach with novel enzyme therapeutics. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

The acquisition or licensing of pharmaceutical products is also very competitive, and a number of more established companies, which have acknowledged strategies to license or acquire products, may have competitive advantages as may other emerging companies taking similar or different approaches to product acquisitions. These established companies may have a competitive advantage over us due to their size, cash flows, and institutional experience.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address rare genetic disease.

With respect to pegzilarginase for Arginase 1 Deficiency, there are currently no effective treatment options or approved therapeutics agents that address the underlying cause of the disease and we are not aware of any other therapeutics that do so in clinical development. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Arginase 1 Deficiency. The current disease management practice for patients with Arginase 1 Deficiency includes dietary protein restriction, essential amino acid supplementation, and ammonia scavengers, which appears to slow the disease progression in some cases. Ammonia scavengers such as Horizon Pharma's RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylbutyrate) are used for the management of elevated blood ammonia in urea cycle disorders in combination with dietary approaches. Erytech Pharma announced a potential collaboration to explore preclinical development of an Arginase 1 Deficiency candidate.

With respect to ACN00177 for Homocystinuria, there is currently one FDA-approved prescription therapy for the treatment of Homocystinuria and several medical foods for the dietary management of individuals with Homocystinuria. The primary treatment goal in patients with Homocystinuria is to maintain consistent plasma tHcy levels as close to normal as possible or, at a minimum, below the currently defined biochemical targets. Current disease management practice for the majority of Homocystinuria patients consists of dietary restriction, vitamin B6, B12, folate supplementation, medical foods, and betaine. CYSTADANE® (betaine anhydrous for oral solution) was approved by the FDA in 1986 for the treatment of Homocystinuria, and Recordati Rare Diseases Inc. currently own the North American marketing rights to this product. Medical foods are manufactured by Breckenridge Pharmaceutical, Inc. and Upsher-Smith Laboratories, LLC.

We are also aware of one investigational therapy in clinical development for the treatment of Homocystinuria. Orphan Technologies Ltd. is enrolling a Phase 1/2 study of OT-58, an enzyme replacement therapy in patients with Cystathionine Beta-Synthase Deficient Homocystinuria. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Homocystinuria.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, nonclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved medicines than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of assays or tests that are essential to identifying an appropriate patient population, which we refer to as companion diagnostics, in guiding the use of related therapeutics, the level of biosimilar competition and the availability of reimbursement from government and other third-party payors.

## **Manufacturing**

We currently contract with third parties for the process development, manufacturing, and testing of our product candidates for nonclinical and clinical studies and intend to do so for future studies as well. We may qualify additional manufacturers to provide potential alternative sources for the active pharmaceutical ingredient and fill-and-finish services for pegzilarginase, ACN00177, and other pipeline candidates as the compounds progress through clinical development. We believe we have sufficient supplies of pegzilarginase for our ongoing Phase 3 pivotal trial in conjunction with the open label extension study for the treatment of patients with Arginase 1 Deficiency and sufficient supplies of ACN00177 for our planned Phase 1/2 clinical trial for the treatment patients with Homocystinuria.

## ***The Diosynth Agreement***

In November 2018, we entered into a master services agreement (Diosynth Agreement) with Fujifilm Diosynth Biotechnologies UK Limited, Fujifilm Diosynth Biotechnologies Texas, LLC, and Fujifilm Diosynth Biotechnologies U.S.A., Inc. (collectively, Fujifilm). Under the Diosynth Agreement, Fujifilm provides research, development, testing and manufacturing services of certain of our products, which are or will be designated as programs pursuant to scope of work agreements. The fees for such services are or will be set out in each scope of work agreement. We may pay additional fees in consideration of certain research and development and technical consultancy services in relation to the procurement, testing and management of consumables, subcontracted work (including delivery of material to and from such subcontractors), process-specific equipment (including installation and qualification thereof), modifications and special waste. Either party may terminate the Diosynth Agreement by giving six months written notice to the other party, provided there are no uncompleted programs existing at the date such notice is given, or upon material breach. We may also be required to pay Fujifilm cancellation fees in the event that we decide to terminate any scope of work prior to its completion, calculated as a percentage of the fees payable under the applicable scope of work agreement. Additionally, upon providing written notice, we may cancel certain stages or programs for convenience, and Fujifilm may terminate for certain unforeseen technical errors.

## **Government Regulation and Product Approval**

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

## ***FDA approval process***

In the United States, pharmaceutical products are subject to extensive regulation by the United States Food and Drug Administration, or the FDA. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, 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 pharmaceutical products. Biological products used for the prevention, treatment, or cure of a disease or condition of a human being are subject to regulation under the FDC Act, except the section of the FDC Act which governs the approval of new drug applications, or NDAs. Biological products are approved for marketing under provisions of the Public Health Service Act, or PHSA, via a Biologics License Application, or BLA. However, the application process and requirements for approval of BLAs are very similar to those for NDAs, and biologics are associated with similar approval risks and costs as drugs. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as clinical hold, FDA refusal to approve pending NDAs or BLAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal prosecution.

Biological product development for a new product or certain changes to an approved product in the United States typically involves preclinical laboratory and animal tests, the submission to the FDA of an investigational new drug application, or IND, which must become effective before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity, and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of some preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. Clinical trials involve the administration of the investigational biologic to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) 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 trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. The trial protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board, or IRB, for approval. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials to support BLAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the biologic into healthy human subjects or patients, the product is tested to assess safety, metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug or biologic for a particular indication, dosage tolerance, and optimal dosage, and to identify common adverse effects and safety risks. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug or biologic and to provide adequate information for the labeling of the product. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the biologic. A single Phase 3 trial with other confirmatory evidence may be sufficient in rare instances where the trial is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

In addition, the manufacturer of an investigational drug in a Phase 2 or Phase 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access to such investigational drug.

After completion of the required clinical testing, a BLA is prepared and submitted to the FDA. FDA approval of the BLA is required before marketing of the product may begin in the United States. The BLA must include the results of all preclinical, clinical, and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting a BLA is substantial. The submission of most BLAs is additionally subject to a substantial application user fee, and the applicant under an approved BLA is also subject to an annual program fee for each prescription product. These fees are typically increased annually. The FDA has 60 days from its receipt of a BLA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of BLAs. Most such applications for standard review biologic products are reviewed within ten months of the date the FDA files the BLA; most applications for priority review biologics are reviewed within six months of the date the FDA files the BLA. Priority review can be applied to a biologic that the FDA determines has the potential to treat a serious or life-threatening condition and, if approved, would be a significant improvement in safety or effectiveness compared to available therapies. The review process for both standard and priority review may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission.

The FDA may also refer applications for novel biologic products, or biologic products that present difficult questions of safety or efficacy, to an advisory committee—typically a panel that includes clinicians and other experts—for review, evaluation, and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the biologic product is manufactured. The FDA will not approve the product unless compliance with current good manufacturing practice, or cGMP, is satisfactory and the BLA contains data that provide substantial evidence that the biologic is safe, pure, potent and effective in the intended indication.

After the FDA evaluates the BLA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the BLA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. An approval letter authorizes commercial marketing of the biologic with specific prescribing information for specific indications. As a condition of BLA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the biologic outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the product. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the product's safety or efficacy.

Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified 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 BLA or BLA supplement before the change can be implemented. A BLA 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 BLA supplements as it does in reviewing BLAs.

### ***Fast track designation and accelerated approval***

The FDA is required to facilitate the development, and expedite the review, of biologics that are intended for the treatment of a serious or life-threatening disease or condition for which there is no effective treatment and which demonstrate the potential to address unmet medical needs for the condition. Under the fast track program, the sponsor of a new biologic candidate may request that the FDA designate the candidate for a specific indication as a fast track biologic concurrent with, or after, the filing of the IND for the candidate. The FDA must determine if the biologic candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request. Under the fast track program and FDA's accelerated approval regulations, the FDA may approve a biologic for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon 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.

In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions, or survives. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. A biologic candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval trials, or confirm a clinical benefit during post-marketing trials, will allow the FDA to withdraw the biologic from the market on an expedited basis. All promotional materials for biologic candidates approved under accelerated regulations are subject to prior review by the FDA.

In addition to other benefits such as the ability to use surrogate endpoints and engage in more frequent interactions with the FDA, the FDA may initiate review of sections of a fast track product's BLA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing an application does not begin until the last section of the BLA is submitted. Additionally, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

### ***Breakthrough therapy designation***

The FDA is also required to expedite the development and review of the application for approval of biological products that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the biologic may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new biologic candidate may request that the FDA designate the candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the biologic candidate. The FDA must determine if the biological product qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request.

### ***Orphan drug designation***

Under the Orphan Drug Act, the FDA may grant orphan drug designation to biological products intended to treat a rare disease or condition—generally a 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, there is no reasonable expectation that the cost of developing and making a product available in the United States for such disease or condition will be recovered from sales of the product.

Orphan drug designation must be requested before submitting a BLA. After the FDA grants orphan drug designation, the generic identity of the biological product and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first BLA applicant to receive FDA approval for a particular active moiety to treat a particular disease with FDA orphan drug designation is entitled to a seven-year exclusive marketing period in the United States for that product for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market a biological product containing the same principal molecular structural features for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. A product is clinically superior if it is safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biological product for the same disease or condition, or the same biological product for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the BLA user fee.

### ***Rare pediatric disease priority review voucher program***

Under the Rare Pediatric Disease Priority Review Voucher program, FDA may award a priority review voucher to the sponsor of an approved marketing application for a product that treats or prevents a rare pediatric disease. The voucher entitles the sponsor to priority review of one subsequent marketing application.

A voucher may be awarded only for an approved rare pediatric disease product application. A rare pediatric disease product application is an NDA or BLA for a product that treats or prevents a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years; in general, the disease must affect fewer than 200,000 such individuals in the U.S.; the NDA or BLA must be deemed eligible for priority review; the NDA or BLA must not seek approval for a different adult indication (i.e., for a different disease/condition); the product must not contain an active ingredient that has been previously approved by FDA; and the NDA or BLA must rely on clinical data derived from studies examining a pediatric population such that the approved product can be adequately labeled for the pediatric population. Before NDA or BLA approval, FDA may designate a product in development as a product for a rare pediatric disease, but such designation is not required to receive a voucher.

To receive a rare pediatric disease priority review voucher, a sponsor must notify FDA, upon submission of the NDA or BLA, of its intent to request a voucher. If FDA determines that the NDA or BLA is a rare pediatric disease product application, and if the NDA or BLA is approved, FDA will award the sponsor of the NDA or BLA a voucher upon approval of the NDA or BLA. FDA may revoke a rare pediatric disease priority review voucher if the product for which it was awarded is not marketed in the U.S. within 365 days of the product's approval.

The voucher, which is transferable to another sponsor, may be submitted with a subsequent NDA or BLA and entitles the holder to priority review of the accompanying NDA or BLA. The sponsor submitting the priority review voucher must notify FDA of its intent to submit the voucher with the NDA or BLA at least 90 days prior to submission of the NDA or BLA and must pay a priority review user fee in addition to any other required user fee. FDA must take action on an NDA or BLA under priority review within six months of receipt of the NDA or BLA.



The Rare Pediatric Disease Priority Review Voucher program was reauthorized in the 21st Century Cures Act, allowing a product that is designated as a product for a rare pediatric disease prior to October 1, 2020 to be eligible to receive a rare pediatric disease priority review voucher upon approval of a qualifying NDA or BLA prior to October 1, 2022.

### ***Disclosure of clinical trial information***

Sponsors of clinical trials of FDA-regulated products, including biological products, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

### ***Pediatric information***

Under the Pediatric Research Equity Act, or PREA, NDAs or BLAs or supplements to NDAs or BLAs must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the biological product is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by statute or regulation, PREA generally does not apply to a drug for an indication for which orphan designation has been granted; however, beginning in 2020, PREA will apply to BLAs for orphan-designated drugs if the drug is a molecularly targeted cancer product intended for the treatment of an adult cancer and is directed at a molecular target that the FDA has determined is substantially relevant to the growth or progression of a pediatric cancer.

### ***Additional controls for biologics***

To help reduce the increased risk of the introduction of adventitious agents and related process impurities, the PHSa emphasizes the importance of manufacturing controls for products whose attributes cannot be precisely defined. The PHSa also provides authority to the FDA to immediately suspend licenses in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases in the United States and between states.

After a BLA is approved, the product may also be subject to official lot release as a condition of approval. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products. As with drugs, after approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

### ***Patent term restoration***

After approval, owners of relevant drug or biologic patents may apply for up to a five year patent extension. The allowable patent term extension is calculated as half of the drug's testing phase—the time between IND application and NDA or BLA submission—and all of the review phase—the time between NDA or BLA submission and approval up to a maximum of five years. The time can be shortened if FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the U.S. PTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug or biologic for which an NDA or BLA has not been submitted.

## **Biosimilars**

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, creates an abbreviated approval pathway for biological products shown to be highly similar to or interchangeable with an FDA-licensed reference biological product. Biosimilarity sufficient to reference a prior FDA-approved product requires that there be no differences in conditions of use, route of administration, dosage form, and strength, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical trials, animal trials, and a clinical trial or trials, unless the Secretary of Health and Human Services waives a required element. A biosimilar product may be deemed interchangeable with a prior approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. The first biosimilar was approved by FDA in 2015, and no interchangeable products have been approved under the BPCIA. Complexities associated with the larger, and often more complex, structures of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation, which is still being evaluated by the FDA.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product, and no application for a biosimilar can be submitted for four years from the date of licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against a finding of interchangeability for other biologics for the same condition of use for the lesser of (i) one year after first commercial marketing of the first interchangeable biosimilar, (ii) 18 months after the first interchangeable biosimilar is approved if there is no patent challenge, (iii) eighteen months after resolution of a lawsuit over the patents of the reference biologic in favor of the first interchangeable biosimilar applicant, or (iv) 42 months after the first interchangeable biosimilar's application has been approved if a patent lawsuit is ongoing within the 42-month period.

## **Post-approval requirements**

Once a BLA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of biologics, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the internet. Biologics may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Adverse event reporting and submission of periodic reports is required following FDA approval of a BLA. The FDA also may require post-marketing testing, known as Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or the FDA may place conditions on an approval that could restrict the distribution or use of the product. In addition, quality control, biological product manufacture, packaging, and labeling procedures must continue to conform to cGMPs after approval. Biologic manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money, and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

## **FDA regulation of companion diagnostics**

If use of an *in vitro* diagnostic is essential to safe and effective use of a drug or biologic product, then the FDA generally will require approval or clearance of the diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. The FDA has generally required *in vitro* companion diagnostics intended to select the patients who will respond to cancer treatment to obtain a pre-market approval, or PMA, for that diagnostic simultaneously with approval of the therapeutic. The review of these *in vitro* companion diagnostics in conjunction with the review of a cancer therapeutic involves coordination of review by the FDA's Center for Drug Evaluation and Research and by the FDA's Center for Devices and Radiological Health. Approval and clearance of a companion diagnostic also requires a high level of coordination between the drug or biologic manufacturer and device manufacturer, if different companies.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to a substantial application fee, which is typically increased annually. In addition, PMAs must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, the applicant must demonstrate that the diagnostic has adequate sensitivity and specificity, has adequate specimen and reagent stability, and produces reproducible results when the same sample is tested multiple times by multiple users at multiple laboratories. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also register their establishment(s), including payment of an annual establishment registration fee, and list their device(s) with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

### ***Other U.S. healthcare laws and compliance requirements***

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, sales, marketing and scientific/educational grant programs must comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term remuneration has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor.

Additionally, the intent standard under the Anti-Kickback Statute was amended by the Affordable Care Act, or ACA, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act (discussed below).

The civil monetary penalties statute imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to, or approval by, the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes “any request or demand” for money or property presented to the U.S. government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies’ marketing of the product for unapproved, and thus generally non-reimbursable, uses.

HIPAA created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA’s privacy and security standards directly applicable to business associates, independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys’ fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act within the ACA, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) to report information related to certain payments or other transfers of value made or distributed to physicians and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. The reported data are posted in searchable form on a public website on an annual basis. Failure to submit required information may result in civil monetary penalties. Effective January 1, 2022, we will also be required to report on transfers of value to physician assistants, nurse practitioners or clinical nurse specialists, certified registered nurse anesthetists, and certified nurse-midwives.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug and biological products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private “qui tam” actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

### ***Coverage, pricing and reimbursement***

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage, and establish adequate reimbursement levels for such products. In the United States, third-party payors include federal and state healthcare programs, private managed care providers, health insurers and other organizations. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical products, therapies and services, in addition to questioning their safety and efficacy. We may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor’s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor’s determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. 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 product development.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product 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 has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any product candidates 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, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on healthcare pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

### ***Healthcare reform***

The ACA has substantially changed some aspects of healthcare financing and delivery by both governmental and private insurers. The ACA has affected existing government healthcare programs and resulted in the development of new programs.

Among the ACA provisions of importance to the pharmaceutical and biotechnology industries, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs, that began in 2011;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP;

- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' 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;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals beginning in 2014 and by adding new mandatory eligibility categories for 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; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

On January 20, 2017, federal agencies with authorities and responsibilities under the ACA were directed to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. More recently, the Tax Cuts and Jobs Act was signed into law in December 2017, which eliminated certain requirements of the ACA, including the individual mandate, and plans to repeal all or portions of the ACA have also been suggested. We cannot predict whether these challenges will continue or whether other proposals will be made or adopted, or what impact these efforts may have on 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.

### ***Additional regulation***

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

### ***Europe / rest of world government regulation***

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Whether or not we obtain FDA approval of a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the EU, for example, a clinical trial application must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the clinical trial application is approved in accordance with a country's requirements, clinical trial development may proceed. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug or biological product under EU regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the EU, with the exception of, among other things, country-specific document requirements.

For other countries outside of the EU, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we or our potential collaborators fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

### **Corporate Information**

We were formed as a limited liability company under the laws of the State of Delaware in December 2013 and converted to a Delaware corporation in March 2015. Our principal executive offices are located at 805 Las Cimas Parkway, Suite 100, Austin, Texas 78746, and our telephone number is (512) 942-2935. Our website address is [www.aegleabio.com](http://www.aegleabio.com). The information contained on, or that can be accessed through, our website is not part of this Annual Report, and you should not consider information on our website to be part of this Annual Report.

### **Employees**

As of December 31, 2019, we had a total of 76 full-time employees. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We have not experienced any work stoppages, and we consider our relations with our employees to be good.

### **Financial Information**

We manage our operations and allocate resources as a single reporting segment. Financial information regarding our operations, assets and liabilities, including our net loss for the years ended December 31, 2019, 2018 and 2017 and our total assets as of December 31, 2019 and 2018, is included in our Consolidated Financial Statements in Item 8 of this Annual Report.

### **Available Information**

We file Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other information with the Securities and Exchange Commission (SEC). Our filings with the SEC are available free of charge on the SEC's website at [www.sec.gov](http://www.sec.gov) and on our website under the "Investors" tab as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

## ITEM 1A. RISK FACTORS

*Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below, together with all of the other information in this annual report on Form 10-K, including our consolidated financial statements and related notes and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” before investing in our common stock. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us. If any of the following risks occur, our business, operating results and prospects could be materially harmed. In that event, the price of our common stock could decline, and you could lose part or all of your investment.*

### Risks Related to Our Business and Industry

***Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.***

We are a clinical-stage biotechnology company. We began operations as a limited liability company in December 2013 and converted to a Delaware corporation in March 2015. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our technology, identifying potential product candidates, undertaking nonclinical studies, and preparing for, commencing and conducting clinical trials of our most advanced product candidate, pegzilarginase.

We have not yet demonstrated our ability to successfully complete a pivotal clinical trial, obtain marketing approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Products, on average, take ten to 15 years to be developed from the time they are discovered to the time they are approved and available for treating patients. Although we have recruited a team that has experience with clinical trials, as a company we have limited experience in conducting clinical trials. In part because of this limited experience, we cannot be certain that planned or ongoing clinical trials will begin or be completed on time, if at all. Consequently, any predictions you make about our future success or viability based on our short operating history to date may not be as accurate as they could be if we had a longer operating history or an established track record in commercializing products or conducting clinical trials.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

***We have no source of product revenue and we have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.***

We have a limited operating history and no approved products. Our ability to generate revenue and become profitable depends upon our ability to successfully complete the development of any of our product candidates, including pegzilarginase, for any of our target indications and to obtain necessary regulatory approvals. To date, we have recognized revenue solely from a fully utilized government grant and have not generated any product revenue. Even if we receive regulatory approval for any of our product candidates, we do not know when these product candidates will generate revenue for us, if at all.

In addition, since inception, we have incurred significant operating losses. For the years ended December 31, 2019, 2018, and 2017, we reported a net loss of \$78.3 million, \$44.3 million and \$27.2 million, respectively. As of December 31, 2019, we had an accumulated deficit of \$195.1 million. We have financed our operations primarily through private placements of our preferred stock, the initial public offering of our common stock, follow-on public offerings of our common stock, and collection of a research grant. We have devoted substantially all of our efforts to research and development. Currently, we are conducting clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency and in a combination clinical trial with pembrolizumab for the treatment of small cell lung cancer, or SCLC. We have concluded enrollment in our combination clinical trial of pegzilarginase with pembrolizumab for the treatment SCLC and are currently exploring partnership opportunities for further development in oncology. We expect to initiate a Phase 1/2 clinical trial for Homocystinuria in the second quarter of 2020, and we have not initiated clinical development of our other product candidates and none of our product candidates are ready for commercialization. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, and the net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- continue our research, nonclinical and clinical development of our product candidates;
- seek to identify additional product candidates;



- conduct additional nonclinical studies and initiate clinical trials for our product candidates;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials, including pivotal trials;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional executive, clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development; and
- acquire or in-license other product candidates and technologies.

We are unable to predict the timing or amount of increased expenses, or when, or if, we will be able to achieve or maintain profitability because of the numerous risks and uncertainties associated with product development. In addition, our expenses could increase significantly beyond expectations if we are required by the FDA, EMA, MHRA, or other relevant regulatory authorities, or the Health Authorities, to modify protocols of our clinical trials or perform studies in addition to those that we currently anticipate. Even if pegzilarginase, or any of our other product candidates, is approved for commercial sale, we anticipate incurring significant costs associated with the commercial launch of any product candidate.

To become and remain profitable, we must develop and eventually commercialize a product candidate or product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing nonclinical testing, initiating and completing clinical trials of one or more of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those product candidates for which we obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. We are currently advancing clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency, expect to initiate a Phase 1/2 for Homocystinuria in the second quarter of 2020, and are in the nonclinical development stages for our remaining product candidates. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain or expand our research and development efforts, expand our business or continue our operations. A decline in the value of our company would also cause you to lose part or even all of your investment.

***We may not be successful in advancing the clinical development of our product candidates, including pegzilarginase.***

In order to execute on our strategy of advancing the clinical development of our product candidates, we are conducting a global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) clinical trial and an ongoing open-label extension study of our completed Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency. We also expect to initiate a Phase 1/2 clinical trial of Homocystinuria in the second quarter of 2020. If our product candidates fail to work as we expect, or if we need to conduct additional studies to better understand the relationship between our product candidates and clinical activity, our ability to assess the therapeutic effect, seek regulatory approval or otherwise begin or further clinical development, could be compromised. For instance, we discontinued clinical development of pegzilarginase for the treatment of the hematological malignancies acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS, in December 2017 due to lack of evidence of clinical benefit. Additionally, we completed our Phase 1 clinical trial of pegzilarginase for the treatment of advanced solid tumors to study small cell lung cancer, uveal melanoma, and cutaneous melanoma and concluded enrollment of our combination trial of pegzilarginase with pembrolizumab for the treatment of patients with SCLC. We are currently exploring partnership opportunities for further development in oncology. Also, while we have shown in our Phase 1/2 trial for the treatment of Arginase 1 Deficiency that a reduction of arginine and its metabolites appears to result in clinical benefit, the Health Authorities may not agree with our assessment. Such an event may result in longer development times, larger trials and a greater likelihood of terminating the trial or not obtaining regulatory approval.

To the extent we pursue oncology-related applications of our product candidates, because the natural history of different tumor types is variable, we will need to study our product candidates in clinical trials specific for a given tumor type and this will result in increased time and cost. If any of our ongoing or planned clinical trials are unsuccessful, our business will suffer.

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

We expect our expenses to increase in parallel with our ongoing activities, particularly as we continue our research and nonclinical development to identify new clinical candidates and initiate and continue clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding to support our continuing operations. If we are unable to raise capital when needed for any reason, including but not limited to a federal government shutdown, or on acceptable terms, we would be forced to delay, reduce or eliminate our discovery and nonclinical development programs, our ongoing clinical development, or any future clinical development or commercialization efforts.

Based upon our planned use of our cash, cash equivalents, marketable securities, and restricted cash as of December 31, 2019, we estimate such funds will be sufficient for us to (i) fund completion of our global pivotal Phase 3 PEACE clinical trial for the treatment of patients with Arginase 1 Deficiency, (ii) fund completion of our ongoing open-label extension study for patients with Arginase 1 Deficiency, and (iii) initiate a Phase 1/2 clinical trial for Homocystinuria. Our future capital requirements will depend on many factors, including:

- the costs associated with the scope, progress and results of compound discovery, nonclinical development, laboratory testing and clinical trials for our product candidates;
- the costs related to the extent to which we enter into partnerships or other arrangements with third parties in order to further develop our product candidates;
- the costs and fees associated with the discovery, acquisition or in-license of product candidates or technologies;
- our ability to establish collaborations on favorable terms, if at all;
- the costs of future commercialization activities, if any, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of product candidates that we do not expect to be commercially available for many years, if at all. Accordingly, we will continue to rely on additional financing to achieve our business objectives, which may not be available to us on acceptable terms, or at all.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity or equity-linked offerings, debt financings, grants from research organizations and license and collaboration agreements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, or if existing holders of warrants exercise their rights to purchase common stock, your ownership interest will be diluted, and the terms of these securities may rank senior to our common stock and include liquidation or other preferences, covenants or other terms that adversely affect your rights as a common stockholder. Further, any future sales of our common stock by us or resale of our common stock by our existing stockholders could cause the market price of our common stock to decline. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock.

***We depend heavily on the success of our most advanced product candidate, pegzilarginase. Existing and future clinical trials of our product candidates, including pegzilarginase, may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.***

We have invested a significant portion of our efforts and financial resources in the nonclinical and clinical development and testing of our most advanced product candidate, pegzilarginase, for the treatment of patients with Arginase 1 Deficiency and in certain oncology trials. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of pegzilarginase. The success of pegzilarginase, ACN00177, and our other product candidates will depend on many factors, including the following:

- successful enrollment of patients in, and the completion of, our ongoing and planned clinical trials, including our global pivotal Phase 3 PEACE clinical trial;
- receiving required regulatory approvals for the development and commercialization of our product candidates as monotherapy or in combination with other products;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our product candidates and their components;
- enforcing and defending intellectual property rights and claims;
- achieving desirable therapeutic properties for our product candidates' intended indications;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with third parties;
- acceptance of our product candidates, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies; and
- maintaining an acceptable safety profile of our product candidates through clinical trials and following regulatory approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

***Clinical drug development involves a lengthy and expensive process with an uncertain outcome. We may experience delays in completing, or ultimately be unable to complete, the development and commercialization of any of our product candidates.***

We have initiated clinical trials with our lead product candidate, pegzilarginase. The risk of failure for all of our product candidates is high. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete nonclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans for the respective target indications. Clinical testing is expensive, difficult to design and implement, can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process.

The results of nonclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials that will likely differ in design and size from early-stage clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, while we have observed a reduction in blood arginine and arginine metabolite levels due to administration of pegzilarginase in patients with Arginase 1 Deficiency, and a reduction in blood arginine levels due to pegzilarginase in patients with advanced solid tumors, this data may not necessarily be predictive of the final results of all patients intended to be enrolled in our ongoing or future clinical trials, and may also not be predictive of pegzilarginase's ability to reduce arginine or arginine metabolite levels for these patients over a longer term nor predictive of positive clinical outcomes. In addition, while we intend to announce interim data from our clinical trials from time to time, such reports may be based on unaudited data provided by our clinical trial investigators. An audit or subsequent review of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we anticipate. In addition, our observations of clinical improvements, through clinician and assessor feedback or assessment tools in the Phase 1/2 open label study of pegzilarginase in patients with Arginase 1 Deficiency after eight and twenty weekly doses, may not be representative of

our observations with subsequently dosed patients out to twenty weeks or longer. We have begun dosing in our single, global pivotal Phase 3 PEACE clinical trial to evaluate the safety and efficacy of pegzilarginase and anticipate that data from the Phase 3 PEACE clinical trial will be available in the first quarter of 2021. Furthermore, while our completed Phase 1/2 clinical trial for the treatment of patients with Arginase 1 Deficiency primarily evaluated the safety of our product candidate, such nonclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in nonclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. Further, while we have conducted prior clinical trials of pegzilarginase in certain oncology indications, we are currently exploring partnership opportunities for further development in oncology. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval.

We may experience delays in our ongoing and planned clinical trials and we do not know whether planned clinical trials will begin or enroll subjects on time, whether enrolled subjects will complete trials on time or at all, whether they will need to be redesigned or whether they will be able to be completed on schedule, if at all. There can be no assurance that the Health Authorities will allow us to begin clinical trials or that they will not put any of the trials for any of our product candidates that enter or have entered clinical development on clinical hold in the future. We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates. Clinical trials may be delayed, suspended or prematurely terminated because costs are greater than we anticipate or for a variety of reasons, such as:

- delay or failure in reaching agreement with the Health Authorities on a trial design that we are able to execute;
- delay or failure in obtaining authorization to commence a trial or inability to comply with conditions imposed by a regulatory authority regarding the scope or design of a clinical trial;
- delays in reaching, or failure to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with planned trial sites;
- modifications to our ongoing and planned clinical trial protocols due to regulatory requirements or decisions made by regulatory authorities;
- geographic complexities of managing the design and completion of clinical trials across different Health Authorities in the United States, Canada, Europe, etc.;
- reports of safety issues, side effects or dose-limiting toxicities, or any additional or more severe safety issues in addition to those observed to date;
- inability, delay, or failure in identifying and maintaining a sufficient number of trial sites, many of which may already be engaged in other clinical programs;
- delay or failure in recruiting and enrolling suitable subjects to participate in one or more clinical trials;
- delay or failure in having subjects complete a trial or return for post-treatment follow-up. For instance, two patients previously dosed in our Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency withdrew from the trial due to personal reasons;
- clinical sites and investigators deviating from the trial protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial;
- a clinical hold for any of our ongoing or planned clinical trials, including for pegzilarginase, where a clinical hold in a trial in one indication could result in a clinical hold for clinical trials in other indications;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct more clinical trials than we anticipate or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or insufficient or participants may drop out of these clinical trials at a higher rate than we anticipate;
- we may experience delays or difficulties in the enrollment of patients, including the identification of patients with Arginase 1 Deficiency and Homocystinuria;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have difficulty partnering with experienced CROs that can run our clinical trials effectively;

- regulators may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks or privacy concerns;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; or
- there may be changes in governmental regulations or administrative actions.

If we are required to modify our ongoing clinical trial protocols, conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully initiate or complete clinical trials of our product candidates or other testing, if the results of these trials or tests do not demonstrate sufficient clinical benefit or if our product candidates do not have an acceptable safety profile, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- cease development of our product candidates;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings that would reduce the potential market for our product candidates or inhibit our ability to successfully commercialize our product candidates;
- be subject to additional post-marketing restrictions and/or testing requirements; or
- have the product removed from the market after obtaining marketing approval.

We do not know whether any of our planned or current nonclinical studies, or ongoing or planned clinical trials, will need to be restructured or will be completed on schedule, or at all. For example, in June 2017, we delayed enrollment of pediatric patients in our Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency due to a difference in opinion with the FDA on data required to support inclusion of pediatric patients. Although we reached an agreement with the FDA in November 2017 and began dosing pediatric patients, the FDA may require additional information or studies to be conducted, or impose conditions that could further delay or restrict our other planned clinical activities in the future. We began our global pivotal Phase 3 PEACE clinical trial in which we are studying plasma arginine reduction from baseline over 24 weeks as our primary endpoint. However, evidence of stabilization or improvement of clinical signs and symptoms of Arginase 1 Deficiency, such as our secondary endpoints, consisting of clinical outcome assessments focused primarily on mobility, as well as clinician and caregiver global impressions of effectiveness, may be required in addition to the primary endpoint to support approval. Certain of our clinical outcome secondary endpoints will be measured using motor assessments that have not been previously validated for Arginase 1 Deficiency, including the gross motor function classification system. Such motor assessments have only been validated in ambulatory children with cerebral palsy. We believe these motor functional assessments are translatable to Arginase 1 Deficiency patients given the similarities in symptoms of children with cerebral palsy and the Arginase 1 Deficiency populations, however the FDA or other Health Authorities may disagree.

We also may face difficulties or delays in enrolling our global pivotal Phase 3 PEACE clinical trial in Arginase 1 Deficiency because we are restricting enrollment to patients with baseline clinical abnormalities at a level that provides an opportunity to demonstrate neuromotor and/or neurocognitive outcomes. If we are unable to demonstrate sufficient improvement on such clinical endpoints, the FDA may determine that there is inadequate justification to support that the endpoints we have chosen are reasonably likely to predict clinical benefit, which would potentially prohibit approval under various approval pathways. For example, the FDA indicated that our dosing duration for our Phase 3 PEACE clinical trial may not be adequate to assess for clinically meaningful changes. Significant nonclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may materially harm our business and results of operations.

***We may not be able to submit INDs, or foreign equivalents outside of the United States, to commence clinical trials for product candidates on the timeframes we expect, and even if we are able to, the Health Authorities may not permit us to proceed with planned clinical trials.***

We are currently conducting nonclinical development of our product candidates other than our clinical trials for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. We submitted a CTA and we expect to initiate a Phase 1/2 clinical trial for Homocystinuria in the second quarter of 2020. Progression of any candidate into clinical trials is inherently risky and dependent on the results obtained in nonclinical programs, and other potential results such as the results of other clinical programs and results of third-party programs. If results are not available when expected or problems are identified during therapy development, we may experience significant delays in clinical development. This may also impact our ability to achieve certain financial milestones and the expected timeframes to market any of our product candidates. Additionally, commencing any future clinical trials is subject to finalizing the trial design and submitting an IND, CTA or comparable submission in other jurisdictions. Even after we submit an IND, CTA or comparable submission in other jurisdictions, the Health Authorities could disagree that we have satisfied their requirements to commence our clinical trials, disagree with our study design, or may change their guidance criteria, which may require us to complete additional nonclinical studies or amend our protocols or impose stricter conditions on the commencement of clinical trials. Failure to submit or have effective INDs, CTAs or other comparable foreign equivalents and commence clinical programs will significantly limit our opportunity to generate revenue.

***Our engineered human enzyme product candidates represent a novel therapeutic approach, which could result in heightened regulatory scrutiny, delays in clinical development, or delays in our ability to achieve regulatory approval or commercialization of our product candidates.***

Engineered human enzyme products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the trial period, the manufacturing and quality control standards required to be met by regulators, the number of patients the Health Authorities will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of engineered human enzyme products, or that the data generated in these trials will be acceptable to the FDA or another applicable regulatory authority to support marketing approval.

***We have only initiated clinical trials for pegzilarginase for the treatment of certain conditions. We have not dosed any of our other product candidates in humans. Our existing and future planned clinical trials may reveal significant adverse events, toxicities or other side effects not seen in our nonclinical studies or early stage clinical trials and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates.***

In order to obtain marketing approval for any of our product candidates, we must demonstrate the safety and efficacy of the product candidate for the relevant clinical indication or indications through nonclinical studies and clinical trials as well as additional supporting data. If our product candidates are associated with undesirable side effects in nonclinical studies or clinical trials, in monotherapy or combination therapy, or have characteristics that are unexpected, we may need to interrupt, delay or abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective.

We are currently conducting clinical trials for pegzilarginase for the treatment of patients with Arginase 1 Deficiency and are in the process of completing our combination clinical trial of pegzilarginase with pembrolizumab in patients with previously-treated small cell lung cancer. Given the nature of the patient populations enrolled in these trials, we have observed and expect to continue to observe serious adverse events that could be related or unrelated to pegzilarginase and could impact the safety or efficacy of pegzilarginase.

In our prior clinical trials of pegzilarginase for the treatment of patients with advanced solid tumors and for the treatment of the patients with hematological malignancies AML and MDS, we have observed serious adverse events in some patients, including death. We have reported results from these trials in which we observed serious adverse events that were considered possibly or probably related to the administration of pegzilarginase including asthenia, fatigue, failure to thrive, hypertension, diarrhea, nausea, vomiting, dehydration, dizziness, intracranial hemorrhage, and encephalopathy. In our combination trial of pegzilarginase and pembrolizumab in patients with previously-treated small cell lung cancer, safety observations were consistent with prior studies of pegzilarginase in patients with cancer.

In a completed Phase 1/2 clinical trial and an ongoing open-label extension study of pegzilarginase for the treatment of patients with Arginase 1 Deficiency, we have observed serious adverse events in some patients, including hypersensitivity and hyperammonemia, which were infrequent, expected and manageable. Hyperammonemia is an important metabolic effect experienced by some patients with Arginase 1 Deficiency. None of the patients in these trials discontinued due to adverse events, while two patients discontinued for non-medical reasons.

Subjects in our ongoing and planned clinical trials with pegzilarginase may suffer minor, significant, serious, or even life-threatening adverse events, including those that are drug-related. Subjects in our ongoing and planned clinical trials may also suffer side effects not yet observed in any of our prior and ongoing clinical or nonclinical studies, including, but not limited to, toxicities to the nervous system, liver, heart, lung, kidney, blood, pulmonary or immune system. We have not dosed any of our other product candidates in humans.

Testing in animals, such as our primate studies for pegzilarginase, may not uncover all side effects in humans or any observed side effects in animals may be more severe in humans. For example, it is possible that patients' immune systems may recognize our engineered human enzymes as foreign and trigger an immune response. This risk is heightened in patients with many genetic enzyme deficiencies who lack the target enzyme, including patients with Arginase 1 Deficiency that we are treating in our global pivotal Phase 3 PEACE trial, our Phase 2 trial open label extension study, and any future clinical trials we conduct for this rare genetic disease. In addition, our product candidates such as pegzilarginase break down target amino acids such as arginine, thereby releasing metabolites such as ornithine into the bloodstream. Some patients may be sensitive to these metabolites, increasing the risk of an adverse reaction due to treatment, which risk may not be able to be mitigated through dosing. Finally, although our engineered human enzyme product candidates such as pegzilarginase are engineered from the human genome, pegzilarginase is produced in *E. coli*. This manufacturing process could lead to the pegzilarginase product being more likely to trigger an immune response than we expect.

To the extent significant adverse events or other side effects are observed in any of our clinical trials, we may have difficulty recruiting patients to the clinical trial, patients may drop out of our trial, or we may be required to abandon the trial or our development efforts of that product candidate altogether. Some potential therapeutics developed in the biotechnology industry that initially showed therapeutic promise in early-stage studies have later been found to cause side effects that prevented their further development. Even if the side effects do not preclude the drug from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. Any of these developments could materially harm our business, financial condition and prospects.

Further, toxicities associated with our product candidates may also develop after regulatory approval and lead to the withdrawal of the product from the market. We cannot predict whether our product candidates will cause organ or other injury in humans that would preclude or lead to the revocation of regulatory approval based on nonclinical studies or early stage clinical testing.

***If we experience delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.***

We may not be able to initiate or continue our ongoing or planned clinical trials if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the Health Authorities. More specifically, many of our product candidates, including pegzilarginase and ACN00177, initially target indications that may be characterized as orphan markets, which can prolong the clinical trial timeline if sufficient patients cannot be enrolled in a timely manner. Arginase 1 Deficiency is a rare disorder, and there are no published reports of disease prevalence. We commissioned a genetic prevalence analysis and based on that analysis estimate the Arginase 1 Deficiency population is greater than 2,500 patients in the global addressable markets. The genetic prevalence-based methodology is intended to account for misdiagnosis of the disease and to address limitations in newborn screening methodology, including naturally low arginine levels in newborns and lack of geographic availability or standardization of testing. Presently, only 34 U.S. states and jurisdictions perform newborn screening for Arginase 1 Deficiency, and newborn screening is not currently widely performed in European countries. Due to screening requirements and enrollment restrictions in our clinical trial protocol, or any additional restrictions that may be imposed by regulatory agencies, not all patients may be eligible for inclusion in our planned global pivotal Phase 3 PEACE clinical trial. To date, we have identified more than 200 patients in the global addressable markets, primarily in the U.S. and Europe. In the U.S. we have identified more than 100 patients, representing a 40% penetration into the genetic prevalent population. Furthermore, we expect to initiate a Phase 1/2 clinical trial for Homocystinuria in the second quarter of 2020, and estimate the patient population to be greater than 5,000 in global addressable markets, but we may not be able to initiate the trial as expected or locate and enroll a sufficient number of eligible patients as required by the Health Authorities, and the necessary regulatory approvals could be delayed or prevented.

Delays in patient enrollment could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical trials altogether.

Patient enrollment is affected by factors including:

- the severity of the disease under investigation;
- the design of the clinical trial protocol;
- the novelty of the product candidate and acceptance by physicians;
- the patient eligibility criteria for the study in question;
- the size of the total patient population;
- the design of the clinical trials;
- the perceived risks and benefits of the product candidate under study;
- the availability and efficacy of competing therapies and clinical trials;
- our payments for conducting clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment with the product candidate; and
- the proximity and availability of clinical trial sites for prospective patients.

In addition, some patients with Arginase 1 Deficiency suffer from heightened levels of ammonia, or hyperammonemia. Horizon Therapeutics plc actively markets both RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylbutyrate) to treat patients with urea cycle disorders suffering from hyperammonemia. Some patients who may be eligible for our ongoing or planned clinical trials may instead pursue treatment for this aspect of their condition by taking RAVICTI (glycerol phenylbutyrate). Our inability to enroll a sufficient number of patients for any of our clinical trials could result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates and in delays to commercially launching our product candidates, if approved, which would cause the value of our company to decline and limit our ability to obtain additional financing.

***The safety or efficacy profile of pegzilarginase, or any current or future product candidates, may differ in combination therapy with other existing or future drugs, and therefore may preclude its further development or approval, which would materially harm our business.***

From time to time, our commercialization strategy may include the combination of our product candidates with third-parties' products or product candidates. For example, we are in the process of completing our combination trial with Merck to evaluate the combination of pegzilarginase with Merck's anti-PD-1 therapy, KEYTRUDA® (pembrolizumab), for the treatment of patients with small cell lung cancer. Such combination studies involve additional risks due to their reliance on circumstances outside our control, such as those relating to the availability and marketability of the third-party product involved in the study. Additionally, we may be unable to secure and maintain a sufficient supply of such third-party products when needed on commercially reasonable terms. Any such shortages could cause us to delay or terminate our combination trials.

It is also difficult to predict the way in which pegzilarginase, or any current or future product candidate, will interact with third-party products used in combination clinical trials. As a result, such combination trials may demonstrate reduced efficacy, increase or exacerbate side effects that have been seen with pegzilarginase, or any current or future product candidate, alone, or result in new side effects that have not previously been identified with pegzilarginase, or any current or future product candidate, alone. In addition, data obtained from any combination trials may be subject to a variety of interpretations. For instance, positive data may not guarantee the ability to move forward due to changes in the competitive or regulatory environment for the treatment of targeted indications, and failure to achieve our primary endpoints may not necessarily preclude a viable commercial path. Any undesirable side effects, lack of efficacy seen in combination trials, changing regulatory and commercial requirements for approval, differing interpretation of clinical data or other unforeseen circumstances may affect our ability to continue with and obtain regulatory approval for the combination therapy, as well as our ability to continue with and obtain regulatory approval for pegzilarginase monotherapy.



Further, evaluating pegzilarginase, or any current or future product candidate, in combination with other products in clinical development may require us to establish collaborations, licensing arrangements or alliances with third parties. There is no assurance that we will be able to enter into such arrangements on favorable terms, or at all.

***Even though we have obtained orphan drug designation for pegzilarginase in the United States and Europe for the treatment of hyperargininemia, we may not obtain or maintain orphan drug exclusivity for pegzilarginase and we may not obtain orphan drug designation or exclusivity for any of our other product candidates or indications.***

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs or biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States. Similarly, the European Commission may designate a product as an orphan drug under certain circumstances.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same disease for that time period. The applicable period is seven years in the United States and ten years in the European Union. The European exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

In March 2015, we obtained orphan drug designation in the United States for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. In July 2016, we also received orphan drug designation in Europe for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. A company that first obtains FDA or EMA approval for a designated orphan drug for the designated rare disease or condition receives orphan drug marketing exclusivity for that drug for the designated disease for a period of seven years in the United States or ten years in the European Union, respectively. This orphan drug exclusivity prevents the FDA or EMA from approving another application, including a Biologics License Application, or BLA, in the United States or a MAA in the European Union, to market a drug containing the same principal molecular structural features for the same orphan indication, except in very limited circumstances, including when the FDA or the EMA concludes that the later drug is safer, more effective or makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation.

Even though we have received orphan drug designation for pegzilarginase for the treatment of Arginase 1 Deficiency in the United States and Europe, we may not be the first to obtain marketing approval for the orphan-designated indication in these jurisdictions due to the uncertainties associated with developing pharmaceutical product candidates. We may also seek to obtain orphan drug designations in other international jurisdictions. However, there is no guarantee that we would be able to do so on a timely basis, or at all. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition or a drug with the same principal molecular structural features can be approved for a different indication. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, even if we intend to seek orphan drug designation for other product candidates or indications, we may never receive such designations or obtain orphan drug exclusivity.

***A Rare Pediatric Disease designation by the FDA does not guarantee that the NDA or BLA for the product will qualify for a priority review voucher upon approval, and it does not lead to a faster development or regulatory review process, or increase the likelihood that any of our product candidates will receive marketing approval.***

Under the Rare Pediatric Disease Priority Review Voucher program, upon the approval of a qualifying BLA or NDA for the treatment of a rare pediatric disease, the sponsor of such an application would be awarded a rare pediatric disease priority review voucher that can be used to obtain priority review for a subsequent BLA or NDA. In September 2018, the FDA notified us that we obtained Rare Pediatric Disease designation for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. If a product candidate is designated before October 1, 2020, as is the case with pegzilarginase, the sponsor of a qualifying NDA or BLA for such a product is eligible to receive a voucher if the NDA or BLA is approved before October 1, 2022. However, there is no guarantee that any of our product candidates will be approved by that date, or at all, and, therefore, we may not be in a position to obtain a priority review voucher prior to expiration of the program, unless Congress further reauthorizes the program. Additionally, designation of a drug for a rare pediatric disease does not guarantee that a BLA will meet the other eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Finally, a Rare Pediatric Disease designation does not lead to faster development or regulatory review of the product, or increase the likelihood that it will receive marketing approval.

***Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.***

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

***We or third parties may not be successful in developing companion diagnostic assays, if required for our product candidates.***

In developing a product candidate for some indications, we may decide to use a biomarker-based test to identify patients for enrollment and, or, monitor patients in clinical trials. In such case, the FDA may require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate. Additionally, clinical trials that utilize a biomarker-based test to select patients are likely to take longer and require additional funding. We do not have experience or capabilities in developing or commercializing these companion diagnostics and plan to rely in large part on third parties to perform these functions. Companion diagnostic assays are subject to regulation by the FDA as medical devices and require separate regulatory approval prior to the use of such diagnostic assays with a therapeutic product candidate. If we, or any third parties that we engage to assist us, are unable to successfully develop companion diagnostic assays for use with our product candidates, or experience delays in development, we may be unable to identify patients with the specific profile targeted by our product candidates for enrollment in our clinical trials. Accordingly, further investment may be required to further develop or obtain the required regulatory approval for the relevant companion diagnostic assay, which would delay or substantially impact our ability to conduct further clinical trials or obtain regulatory approval. In addition, if a companion diagnostic is necessary for any of our product candidates, the delay or failure to obtain regulatory approval of the companion diagnostic would delay or prevent the approval of the therapeutic product candidate. Alternatively, we may also make the decision that our therapy does not require a companion diagnostic, however the Health Authorities may disagree and require the development and regulatory approval of a companion diagnostic assay as a condition of approval of the product candidate, creating additional costs and a delay in bringing our product candidate to market.

***If the market opportunities for our product candidates are smaller than we believe they are, our future product revenues may be adversely affected and our business may suffer.***

Our understanding of both the number of people who suffer from conditions such as Arginase 1 Deficiency or Homocystinuria, as well as the potential subset of those who have the potential to benefit from treatment with our product candidates, are based on estimates. We expect our product candidates targeting rare diseases to target the smaller patient populations that suffer from the respective diseases we seek to treat. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, Europe or elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our product candidates or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive our potential product candidates less than the potentially addressable market. These include the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Additionally, our assumptions regarding the addressable market may be incorrect and the addressable market may change over time, including from the announcement date of a product candidate to the approval by Health Authorities and commercialization. Even if we obtain significant market share for our product candidates, because certain of the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

***Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.***

Even if any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success. Current treatments for Arginase 1 Deficiency and Homocystinuria include dietary protein restrictions and for Arginase 1 Deficiency, in some instances, nitrogen-scavenging drugs such as RAVICTI (glycerol phenylbutyrate). If our product candidates do not achieve an adequate level of acceptance, we may never generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- their efficacy, safety and other potential advantages compared to alternative treatments;
- our ability to offer them for sale at competitive prices;
- their convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the ability of healthcare professionals to accurately identify and diagnose patients with the relevant/indicated condition;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement for our product candidates;
- the prevalence and severity of their side effects;
- any restrictions on the use of our product candidates together with other medications;
- interactions of our product candidates with other products patients are taking; and
- inability of patients with certain medical histories to take our product candidates.

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

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of product candidate development, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution.

We currently do not have a marketing or sales team for the marketing, sales and distribution of any of our product candidates that are potentially able to obtain regulatory approval. In order to commercialize any product candidates, we must build on a territory-by-territory basis marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. If our product candidates receive regulatory approval, we intend to establish an internal sales or marketing team with technical expertise and supporting distribution capabilities to commercialize our product candidates, which will be expensive and time consuming and will require significant attention of our executive officers to manage. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of any of our product candidates that we obtain approval to market.

With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. We may have little or no control over the marketing and sales efforts of such third parties and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. If we are unable to enter into such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a public company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

***We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.***

The biotechnology and pharmaceutical industries are intensely competitive. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, biotechnology companies, universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations and well-established sales forces. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing, on an exclusive basis, product candidates that are more effective or less costly than any product candidate that we are currently developing or that we may develop.

We face intense competition from companies developing products to address urea cycle disorders and other diseases. For example, Horizon Therapeutics plc actively markets both RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylbutyrate), which is used to treat patients with urea cycle disorders suffering from hyperammonemia, which may include patients suffering from Arginase 1 Deficiency. Patients with Arginase 1 Deficiency may also benefit from taking RAVICTI (glycerol phenylbutyrate). Erytech Pharma announced a potential collaboration to explore preclinical development of an Arginase 1 Deficiency candidate. Polaris Group has been conducting numerous clinical trials of ADI-PEG 20, an enzyme derived from mycoplasma, which degrades arginine in the blood.

We also anticipate a competitive landscape in Homocystinuria. There is currently one FDA-approved therapy for the treatment of Homocystinuria and multiple medical foods. CYSTADANE® (betaine anhydrous for oral solution) was approved by the FDA in 1986 and is currently marketed in North America by Recordati Rare Diseases Inc. We are also aware of one investigational therapy in clinical development for the treatment of Homocystinuria. Orphan Technologies Ltd. is enrolling a Phase 1/2 study of OT-58, an enzyme replacement therapy, in patients with Cystathionine Beta-Synthase Deficient Homocystinuria. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Homocystinuria.

Our ability to compete successfully will depend largely on our ability to leverage our experience in product candidate discovery and development to:

- discover and develop product candidates that are superior to other products in the market;
- attract qualified management, scientific, product development and commercial personnel;
- obtain and maintain patent and/or other proprietary protection for our product candidates and technologies;
- obtain required regulatory approvals; and
- successfully collaborate with research institutions or pharmaceutical companies in the discovery, development and commercialization of new product candidates.

The availability and price of our competitors' products could limit the demand, and the price we are able to charge, for any of our product candidates, if approved. We will not achieve our business plan if acceptance is inhibited by price competition or the reluctance of physicians to switch from existing drug products or other therapies to our product candidates, or if physicians switch to other new drug products or choose to reserve our product candidates for use in limited circumstances.

Established biotechnology companies may invest heavily to accelerate discovery and development of products that could make our product candidates less competitive. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA or non-U.S. regulatory approval or discovering, developing and commercializing product candidates before we do, which would have a material adverse impact on our business. In addition, approved products may be used outside of the approved patient population, particularly in cancer, where approved drugs often receive preferential commercial and regulatory treatment on new indications and alternative lines of therapy. Many of our competitors have greater resources than we do and have established sales and marketing capabilities, whether internally or through third parties. We will not be able to successfully commercialize our product candidates without establishing sales and marketing capabilities internally or through strategic partners.

***The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current product candidates could limit our ability to market those product candidates and decrease our ability to generate revenue.***

The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates that receive marketing approval will depend substantially, both in the United States and internationally, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services since CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for novel products such as ours since there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the European Union, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In general, the prices of products under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Moreover, increasing efforts by governmental and third-party payors, in the United States and internationally, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. The U.S. government has similarly expressed concerns over the pricing of pharmaceutical products and there can be no assurance as to how this scrutiny will impact future pricing of pharmaceutical products generally. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market.

In addition to CMS and private payors, professional organizations such as the National Comprehensive Cancer Network and the American Society of Clinical Oncology can influence decisions about reimbursement for new products by determining standards for care. In addition, many private payors contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our product candidates.

Furthermore, some of our target indications, including for Arginase 1 Deficiency for pegzilarginase, are orphan indications where patient populations are small. In order for therapeutics that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such therapeutics must be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product candidate that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement for any future product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved, and ultimately our financial results.

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

We are a clinical-stage biotechnology company with a limited operating history, and, as of December 31, 2019, had 76 employees, including five executive officers. We are highly dependent on the research and development, clinical and business development expertise of our executive officers, as well as the other principal members of our management, scientific and clinical team. Any of our management team members may terminate their employment with us at any time. We do not maintain “key person” insurance for any of our executives or other employees.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, facilitate regulatory approval of and commercialize product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions.

In addition, we rely on consultants and advisors, including scientific and clinical advisors such as our scientific advisory board, to assist us in formulating our discovery and nonclinical and clinical development and commercialization strategy. Our consultants and advisors, including members of our scientific advisory board, may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

***Our product candidates for which we intend to seek approval as biologic products may face competition sooner than anticipated.***

With the enactment of the Biologics Price Competition and Innovation Act of 2009, or BPCIA, an abbreviated pathway for the approval of biosimilar biological products (both highly similar and interchangeable biological products) was created. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing reference product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the first licensure of date of the reference product licensed under a BLA. On March 6, 2015, the FDA approved the first biosimilar product under the BPCIA. However, the law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when the processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our biological products.

A biological product submitted for licensure under a BLA is eligible for a period of exclusivity that commences on the date of its licensure, unless its date of licensure is not considered a date of first licensure because it falls within an exclusion under the BPCIA. There is a risk that this exclusivity could be shortened due to congressional action or otherwise, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not apply to companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Most states have enacted substitution laws that permit substitution of only interchangeable biosimilars. The extent to which a highly similar biosimilar, once approved, will be substituted for any one of our reference products that may be approved in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

***We may not be successful in our efforts to identify additional product candidates. Due to our limited resources and access to capital, we must prioritize development of certain product candidates, which may prove to be wrong and may adversely affect our business.***

Although we intend to explore other therapeutic opportunities, in addition to the product candidates that we are currently developing, we may fail to identify viable new product candidates for clinical development for a number of reasons. If we fail to identify additional potential product candidates, our business could be materially harmed.

Research programs to pursue the development of our existing and planned product candidates for additional indications and to identify new product candidates and disease targets require substantial technical, financial and human resources whether or not they are ultimately successful. Our research programs may initially show promise in identifying potential indications and/or product candidates, yet fail to yield results for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential indications and/or product candidates;
- potential product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs;
- it may take greater human and financial resources than we will possess to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, thereby limiting our ability to develop, diversify and expand our product portfolio; or
- alternative research or therapeutic methodologies may be more efficient than the research approaches provided by Aeglea.

Because we have limited financial and human resources, we intend to initially focus on research programs and product candidates for a limited set of indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential or a greater likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Accordingly, there can be no assurance that we will ever be able to identify additional therapeutic opportunities for our product candidates or to develop suitable potential product candidates through internal research programs, which could materially adversely affect our future growth and prospects. We may focus our efforts and resources on potential product candidates or other potential programs that ultimately prove to be unsuccessful.

***If we fail to develop additional product candidates, our commercial opportunity will be limited.***

Developing and obtaining regulatory approval for and commercializing any additional product candidates we identify will require substantial additional funding and is prone to the risks of failure inherent in medical product development. We cannot provide you any assurance that we will be able to successfully advance additional product candidates, if any, through the development process.

Even if we receive FDA approval to market additional product candidates for the treatment of the diseases we target, we cannot assure you that any such product candidates will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. If we are unable to successfully develop and commercialize additional product candidates, our commercial opportunity will be limited. Moreover, a failure in obtaining regulatory approval of additional product candidates may have a negative effect on the approval process of other product candidates of ours or result in losing approval of any approved product candidate.

***Our information technology systems, or those used by our CROs, contractors or consultants, may fail or suffer security breaches, which could harm our business and operations.***

Cyberattacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Despite the implementation of security measures, our information technology systems and those of our strategic partners and third-parties on whom we rely are vulnerable to cyberattacks, damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. Furthermore, we have little or no control over the security measures and computer systems of third parties including any CROs we may work with in the future. While we and, to our knowledge, our third-party strategic partners have not experienced any such system failure, accident or security breach to date, if such an event were to occur, it could result in material negative consequences for us including interruptions in our operations, the operations of our strategic partners, or our manufacturers or suppliers, misappropriation of confidential business information and trade secrets, disclosure of corporate strategic plans, and result in material disruptions of our product candidate development programs. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts, and we may incur substantial costs to attempt to recover or reproduce the data. If any disruption or security breach resulted in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability or the further development of our product candidates could be delayed.

***We depend on our information technology and infrastructure.***

We rely on the efficient and uninterrupted operation of information technology systems to manage our operations, to process, transmit, and store electronic and financial information, and to comply with regulatory, legal and tax requirements. We also depend on our information technology infrastructure for communications among our personnel, contractors, consultants and suppliers. System failures or outages could materially compromise our ability to perform these functions in a timely manner, which could harm our ability to conduct business or delay our financial reporting. In addition, we depend on third parties to operate and support our information technology systems. Failure by these providers to adequately deliver the contracted services could have an adverse effect on our business, which in turn may materially adversely affect our operating results and financial condition.

**Risks Related to Our Reliance on Third Parties**

***We currently rely and will rely on third parties to conduct our ongoing and future planned clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.***

We currently rely and will continue to rely on third parties to provide manufacturing and clinical development capabilities. For example, we currently rely on third party contract manufacturing organizations, to manufacture and supply nonclinical and clinical trial quantities of the biological substance of our lead product candidate, pegzilarginase, ACN00177 in Homocystinuria, and for additional pipeline product candidates. We also expect to continue to rely on such third parties to manufacture and supply commercial quantities of pegzilarginase, as well as ACN00177 for our anticipated Phase 1/2 clinical trial.

We rely on third-party CROs to conduct our ongoing and future planned clinical trials of pegzilarginase. We do not plan to independently conduct clinical trials of our other product candidates. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our ongoing and future planned clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with regulatory standards, commonly referred to as good clinical practices for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Other countries' regulatory agencies also have requirements for clinical trials with which we must comply. We also will be required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, *ClinicalTrials.gov*, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.



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

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

***We contract with third parties for the manufacture of our product candidates for nonclinical studies and our ongoing and future planned clinical testing and expect to continue to do so for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates at an acceptable cost and quality, which could delay, prevent or impair our development or commercialization efforts.***

We do not own or operate facilities for the manufacture of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. We rely, and expect to continue to rely, on third parties, for the manufacture of our product candidates for nonclinical studies and for our existing and future planned clinical trials. We also expect to rely on third parties, for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a source for bulk drug substance. Currently, third party manufacturers are supplying, and are expected to continue to supply, the drug substance requirements for our ongoing and planned clinical trials with pegzilarginase. If such third party manufacturers cannot supply us with sufficient amounts, pursuant to product requirements as agreed, we may be required to identify alternative manufacturers, which would lead us to incur added costs and delays in identifying and qualifying any replacement.

The formulation used in early studies is not a final formulation for commercialization. If we are unable to demonstrate that our commercial scale product is comparable to the product used in clinical trials, we may not receive regulatory approval for that product without additional clinical trials. We have contracted with third party manufacturers for certain studies related to potential commercial scale manufacturing of pegzilarginase, but there is no guarantee that such studies, the transfer of technology to or any potential manufacturing at such facility, will be completed successfully, on time, or at all. We also cannot guarantee that we will be able to make any required modifications within currently anticipated timeframes or that such modifications, if and when made, will obtain regulatory approval or that the new processes or modified processes will be successfully implemented by or transferred to any third-party contract suppliers within currently anticipated timeframes. These may require additional studies, and may delay our clinical trials and/or commercialization.

We expect to rely on third-party manufacturers, or third-party strategic partners for the manufacture of commercial supply of any product candidates for which our strategic partners or we obtain marketing approval. We may be unable to establish any additional agreements with third-party manufacturers, or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers on acceptable terms, such third-party manufacturers may have limited experience manufacturing pharmaceutical drugs for commercialization, and reliance on third-party manufacturers for the commercial supply of our products may expose us to various risks, including:

- possible noncompliance by the third party with regulatory requirements and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, or similar regulatory requirements outside the United States. Although we do not have day-to-day control over third-party manufacturers' compliance with these regulations and standards, we are responsible for ensuring compliance with such regulations and standards. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates, operating restrictions and criminal prosecutions, any of which would significantly and adversely affect supplies of our product candidates and our business. If a third-party manufacturer's facilities do not pass a pre-approval inspection or do not have a cGMP compliance status acceptable to the FDA or a comparable foreign regulatory agency, our product candidate will not be approved.

In addition, the process of manufacturing and administering our product candidates is complex and highly regulated. As a result of the complexities, our manufacturing and supply costs are likely to be higher than those at more traditional manufacturing processes and the manufacturing process is less reliable and more difficult to reproduce.

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

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

***Failure of any future third-party collaborators to successfully commercialize companion diagnostics developed for use with our therapeutic product candidates could harm our ability to commercialize these product candidates.***

We do not plan to develop companion diagnostics internally and, as a result, we are dependent on the efforts of our third-party strategic partners to successfully commercialize any needed companion diagnostics. Our strategic partners:

- may not perform their obligations as expected;
- may encounter production difficulties that could constrain the supply of the companion diagnostics;
- may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community;
- may not pursue commercialization of any companion diagnostics;
- may elect not to continue or renew commercialization programs based on changes in the strategic partners' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- may not commit sufficient resources to the marketing and distribution of such companion diagnostic product candidates; and
- may terminate their relationship with us.

If companion diagnostics needed for use with our therapeutic product candidates fail to gain market acceptance, our ability to derive revenues from sales of these therapeutic product candidates could be harmed. If our strategic partners fail to commercialize these companion diagnostics, it could adversely affect and delay the development or commercialization of our therapeutic product candidates.

***We may not be successful in finding strategic partners for continuing development of certain of our product candidates or successfully commercializing or competing in the market for certain indications.***

We may seek to develop strategic partnerships for developing certain of our product candidates, due to capital costs required to develop the product candidates or manufacturing constraints. We may not be successful in our efforts to establish such a strategic partnership or other alternative arrangements for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy. In addition, we may be restricted under existing collaboration agreements from entering into future agreements with potential strategic partners. We cannot be certain that, following a strategic transaction or license, we will achieve an economic benefit that justifies such transaction.

If we are unable to reach agreements with suitable strategic partners on a timely basis, on acceptable terms or at all, we may have to curtail the development of a product candidate, reduce or delay its development program, delay its potential commercialization, reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates and our business, financial condition, results of operations and prospects may be materially and adversely affected.

***Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.***

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to (i) comply with FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, (ii) provide accurate information to the FDA or comparable non-U.S. regulatory authorities, (iii) comply with manufacturing standards we have established, (iv) comply with the Foreign Corrupt Practices Act and federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable non-U.S. regulatory authorities, or (v) report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

***If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.***

We face an inherent risk of product liability as a result of testing our product candidates in clinical trials and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical trials, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- inability to bring a product candidate to the market;
- decreased demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;

- diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- decline in our share price.

Our product liability insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

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

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

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property.

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

***We and our strategic partners that we rely on may be adversely affected by natural disasters, and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.***

Natural disasters could severely disrupt our operations or the operations of our third party manufacturers' facilities and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters or research laboratory, that damaged critical infrastructure, such as our third party manufacturers' facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and may not prove adequate in the event of a serious disaster or similar event. Substantially all of our current supply of product candidates are located at a single third party manufacturer's facilities, and we do not have any existing back-up facilities in place or plans for such back-up facilities. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

## Risks Related to Government Regulation

***If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals in the United States or in foreign jurisdictions, we will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.***

Our product candidates must be approved by the FDA pursuant to a BLA in the United States, and by the EMA pursuant to a MAA, and by other comparable regulatory authorities outside the United States prior to commercialization. The process of obtaining marketing approvals, both in the United States and internationally, is expensive and takes many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval in Europe or another non-U.S. jurisdiction may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our third-party strategic partners may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. Furthermore, the implementation of Brexit may disrupt the operation of any pre-and post-authorization clinical trial infrastructure and regulatory frameworks in Europe, as discussed further below. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our product candidates in any market.

Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have no experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing marketing approval requires the submission of extensive nonclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional nonclinical, clinical or other studies. In addition, varying interpretations of the data obtained from nonclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may also cause delays in or prevent the approval of an application.

Approval of our product candidates may be delayed or refused for many reasons, including the following:

- the Health Authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the Health Authorities that our product candidates are safe and effective for any of their proposed indications;
- the results of clinical trials may not meet the level of statistical significance required by the Health Authorities for approval;
- we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks;
- the Health Authorities may disagree with our interpretation of data from nonclinical programs or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the Health Authorities to support the submission of a BLA, MAA or other comparable submission in other jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the potential disruptions and uncertainty caused by Brexit implementation, as discussed below;
- the facilities of the third-party manufacturers with which we partner may not be adequate to support approval of our product candidates; and
- the approval policies or regulations of the Health Authorities may significantly change in a manner rendering our clinical data insufficient for approval.

New products for the treatment of cancer frequently are initially indicated only for patient populations that have not responded to an existing therapy or have relapsed. If any of our product candidates receives marketing approval, the approved labeling may limit the use of our product candidates in this way, which could limit sales of the product. Also, any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Additionally, the implementation of the United Kingdom's exit from the European Union, or "Brexit", may cause disruptions and uncertainty in the current regulatory framework in Europe. Brexit has resulted in the EMA moving from the United Kingdom to the Netherlands. In the United Kingdom, this transition may cause disruption in the administrative and medical scientific links between the EMA and MHRA. Following the United Kingdom's departure from the European Union, it no longer automatically complies with the standards of clinical efficacy, safety and chemistry control, and manufacture as applied by the European Medicines Directive. Applications submitted for marketing authorization under the centralized EMA procedure will no longer be automatically validated for authorization in the United Kingdom, and the benefit-risk assessments conducted by the United Kingdom may not be consistent with the EMA conclusions. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the European Union and/or the United Kingdom. In view of the current lack of detail and resolution with regard to the Brexit transition, we are unable to confidently predict the effects of such disruption to the regulatory framework in Europe, and as to how this may delay or impair any potential regulatory approvals, commercialization of any of our product candidates, and our ability to generate potential revenues. If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

***Any Fast Track Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval.***

We have received Fast Track Designation from the FDA for our lead product candidate pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency, and may seek such designation for some or all of our product candidates. If a drug or biologic is intended for the treatment of a serious or life-threatening condition and the drug or biologic demonstrates the potential to address unmet medical needs for this condition, the drug or biologic sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether or not to grant this designation. Even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even though we have received Fast Track Designation for pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency, and even if we receive Fast Track Designation for other product candidates or indications in the future, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many drugs or biologics that have received Fast Track Designation have failed to obtain approval.

We may also seek accelerated approval for products. Under the FDA's accelerated approval program, the FDA may approve a drug or biologic for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon 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. For drugs or biologics granted accelerated approval, post-marketing confirmatory trials are required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence and, in some cases, the FDA may require that the trial be designed and/or initiated prior to approval. Moreover, the FDA may withdraw approval of our product candidate or indication approved under the accelerated approval pathway if, for example:

- the trial or trials required to verify the predicted clinical benefit of our product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug;
- other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use;
- we fail to conduct any required post-approval trial of our product candidate with due diligence; or
- we disseminate false or misleading promotional materials relating to the relevant product candidate.

***A Breakthrough Therapy Designation by the FDA, even if granted for any of our product candidates, may not lead to a faster development or regulatory review or approval process, and does not increase the likelihood that our product candidates will receive marketing approval.***

We have received Breakthrough Therapy Designation from the FDA for our lead product candidate pegzilarginase for the treatment of Arginase 1 Deficiency, and may seek such designation for some or all of our product candidates. A Breakthrough Therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over existing therapies with respect to one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs or biologics that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor can help to identify the most efficient path for development.

Designation as a Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe, after completing early clinical trials, that one of our product candidates meets the criteria for designation as a Breakthrough Therapy, the FDA may disagree and instead determine not to make such designation. Even though we have received Breakthrough Therapy Designation for pegzilarginase for the treatment of Arginase 1 Deficiency, or even if we receive Breakthrough Therapy Designation for other product candidates or indications in the future, we may not experience a faster development process, review or approval compared to drugs or biologics considered for approval under conventional FDA procedures and such a designation does not assure ultimate approval by the FDA. In addition, even though we have received Breakthrough Therapy Designation for pegzilarginase for the treatment of Arginase 1 Deficiency, or if one or more of our other product candidates qualify as Breakthrough Therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

***We may seek priority review designation for one or more of our other product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.***

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the application for such product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review for applications for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review designation to an application, so even if we believe an application for a particular product candidate is eligible for such designation, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in an expedited regulatory review or approval process or confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

***Any product candidate for which we obtain marketing approval will be subject to extensive post-approval marketing regulatory requirements and could be subject to post-approval marketing restrictions or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.***

Our product candidates and the activities associated with their development and commercialization, including their testing, manufacture, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, including periodic inspections by the FDA and other regulatory authorities, requirements regarding the distribution of samples to physicians and recordkeeping.

The FDA closely regulates the post-approval marketing and promotion of drugs and biologics to ensure drugs and biologics are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding use of their products and if we promote our product candidates beyond their approved indications, we may be subject to enforcement action for off-label promotion. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws.

The FDA may also impose requirements for costly post-approval marketing studies or clinical trials and surveillance to monitor the safety or efficacy of any approved product. In particular, certain of our product candidates, if approved, are expected to be dosed chronically, and therefore could require follow-up studies and close monitoring of our patients after regulatory approval has been granted, to establish broader, longer-term understanding of potential for adverse effects than is plausible for clinical research. These studies may be expensive and time-consuming to conduct and may reveal side effects or other harmful effects in patients that use our therapeutic products after they are on the market, which may result in the limitation or withdrawal of our drugs from the market. Alternatively, we may not be able to conduct such additional clinical trials, which might force us to abandon our efforts to develop or commercialize certain product candidates. Even if post-approval studies are not requested or required, after our products are approved and on the market, there might be safety issues that emerge over time that require a change in product labeling or that require withdrawal of the product from the market, which would cause our revenue to decline. If we fail to comply with any such post-approval regulatory requirements, approval for our products may be withdrawn, and product sales may be suspended. We may not be able to regain compliance, or we may only be able to regain compliance after a lengthy delay, significant expense, lost revenues and damage to our reputation.

In addition, later discovery of previously unknown adverse events or other problems with our product candidates, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such product candidates, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of any approved product from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of product candidates;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our product candidates;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Non-compliance with European requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with Europe's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

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

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

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



- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or *qui tam* actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- federal law requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals, which includes annual data collection and reporting obligations, with reported information disclosed on a searchable website on an annual basis; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

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

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

***We are subject to a variety of privacy and data security laws, and our failure to comply with them could harm our business.***

We maintain a large quantity of sensitive information, including confidential business and patient health information in connection with our clinical trials, and are subject to laws and regulations governing the privacy and security of such information. In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws, and federal and state consumer protection laws. Each of these laws is subject to varying interpretations and constantly evolving. In May 2018, a new privacy regime, the General Data Protection Regulation, or GDPR, took effect in the European Economic Area, or EEA. The GDPR increases our obligation with respect to clinical trials conducted in the EEA by expanding the definition of personal data and requiring changes to informed consent practices, as well as more detailed notices for clinical trial subjects and investigators. In addition, the GDPR increases the scrutiny of transfers of personal data from clinical trial sites located in the EEA to the United States, and imposes substantial fines for breaches and violations. Furthermore, any potential effects due to Brexit may cause uncertainty in such regulatory framework. While the government of the United Kingdom has stated that the United Kingdom will still abide with the provisions of the GDPR, uncertainty and disruptions may still occur, and we are currently unable to predict any potential disruptions to such regulatory frameworks. Compliance with these privacy and data security laws and regulations is a rigorous and time-intensive process and if we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, final condition and results of operations.

***Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.***

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved product candidates. While the MMA only applies to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the ACA of importance to our potential product candidates are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate 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;
- a Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability to managed care utilization;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report financial arrangements with physicians and teaching hospitals;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On January 20, 2017, federal agencies with authorities and responsibilities under the ACA were directed to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. More recently, the Tax Cuts and Jobs Act was signed into law, which eliminated certain requirements of the ACA, including the individual mandate, and plans to repeal all or portions of the ACA have also been suggested. We cannot predict whether these challenges will continue or whether other proposals will be made or adopted, or what impact these efforts may have on us.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product candidates.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

***Comprehensive tax reform bills could increase the tax burden on our orphan drug programs and adversely affect our business and financial condition.***

In December 2017, the U.S. government enacted comprehensive tax legislation that includes significant changes to the taxation of business entities. These changes include, among others, (i) a permanent reduction to the corporate income tax rate, (ii) a partial limitation on the deductibility of business interest expense, (iii) a shift of the U.S. taxation of multinational corporations from a tax on worldwide income to a territorial system (along with certain rules designed to prevent erosion of the U.S. income tax base) and (iv) a one-time tax on accumulated offshore earnings held in cash and illiquid assets, with the latter taxed at a lower rate.

Further, the comprehensive tax legislation, among other things, reduces the orphan drug credit from 50% to 25% of qualifying expenditures. When and if we become profitable, this reduction in tax credits may result in an increased federal income tax burden on our orphan drug programs as it may cause us to pay federal income taxes earlier under the revised tax law than under the prior law and, despite being partially off-set by a reduction in the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, may increase our total federal tax liability attributable to such programs.

Notwithstanding the reduction in the corporate income tax rate, the overall impact of this tax reform is uncertain, and our business and financial condition could be adversely affected. In addition, it is uncertain if and to what extent various states will conform to the newly enacted federal tax law.

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance that we believe is consistent with industry norms to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, we cannot assure you that it will be sufficient to cover our liability in such cases. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

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

## Risks Related to Our Intellectual Property

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

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technology and product candidates.

In particular, our success depends in large part on our ability, and our licensors' ability, to obtain and maintain patent protection in the United States and other countries with respect to our proprietary technology and product candidates, including any companion diagnostic developed by us or a third-party strategic partner. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates, and rely on our licensors to obtain patent protection for our licensed intellectual property. Our patent portfolio includes patents and patent applications we own or we exclusively license from the University of Texas at Austin. This patent portfolio includes issued patents and pending patent applications covering compositions of matter and methods of use.

The patent prosecution process is expensive and time-consuming, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner, or in all jurisdictions. We may choose not to seek patent protection for certain innovations and may choose not to pursue patent protection in certain jurisdictions, and under the laws of certain jurisdictions, patents or other intellectual property rights may be unavailable or limited in scope. It is also possible that we will fail to identify patentable aspects of our discovery and nonclinical and clinical development output before it is too late to obtain patent protection. Moreover, the risks pertaining to our patents and intellectual property rights also apply to the intellectual property rights that we license from third parties. In some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. We may also require the cooperation of our licensors in order to enforce the licensed patent rights, and such cooperation may not be provided. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business and the rights we have licensed may be reduced or eliminated.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. The U.S. Patent and Trademark Office, or U.S. PTO, has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents. In addition, the laws of foreign jurisdictions may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions, nor can we know whether those from whom we license patents were the first to make the inventions claimed or were the first to file. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and product candidates. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, during prosecution of any patent application, the issuance of any patents based on an application may depend upon our ability to generate additional nonclinical or clinical data that supports the patentability of our proposed claims. We may not be able to generate such data on a timely basis, to the satisfaction of the U.S. PTO, or at all.

Moreover, we may be subject to a third-party preissuance submission of prior art to the U.S. PTO or patent offices in foreign jurisdictions, or become involved in opposition, derivation, reexamination, inter partes review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize product candidates without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or product candidates in a non-infringing manner.

The issuance of a patent, while given the presumption of validity under the law, is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and product candidates, or limit the duration of the patent protection of our technology and product candidates. In addition, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after the first non-provisional filing in the patent family. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours.

Any inability on our part to adequately protect our intellectual property may have a material adverse effect on our business, operating results and financial position.

***Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.***

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the U.S. PTO and various governmental patent agencies outside the United States in several stages over the lifetime of the patents and/or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, we also rely on licensors to effect such payments with respect to the patents and patent applications that we in-license. Moreover, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

***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 collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference or derivation proceedings before the U.S. PTO and similar bodies in other jurisdictions. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future.

It is also possible that we have failed to identify relevant third-party patents or applications. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of a current or future product candidate, or we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, our products or the use of our products.

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

***We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information or trade secrets of third parties or that our employees, consultants or independent contractors have wrongfully used or disclosed alleged trade secrets of former or other employers.***

Many of our employees, independent contractors and consultants, including our senior management, have been previously employed or retained by universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Further, many of our consultants are currently retained by other biotechnology or pharmaceutical companies and may be subject to conflicting obligations to these third parties. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of third parties in their work for us, and do not perform work for us that is in conflict with their obligations to another employer or any other entity, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise improperly used or disclosed confidential information, including trade secrets or other proprietary information, of a former employer or other third parties. We may also be subject to claims that an employee, advisor, consultant, or independent contractor performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. We are not aware of any threatened or pending claims related to these matters, but in the future litigation may be necessary to defend against such claims.

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

If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable personnel or intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. As a result, we may also elect to enter into license agreements in order to settle patent infringement claims or to resolve disputes prior to litigation, and any such license agreements may require us to pay royalties and other fees that could be significant. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

***The illegal distribution and sale by third parties of counterfeit versions of our products or stolen products could have a negative impact on our reputation and business.***

Third parties might illegally distribute and sell counterfeit or unfit versions of our products, which do not meet our rigorous manufacturing and testing standards. A patient who receives a counterfeit or unfit drug may be at risk for a number of dangerous health consequences. Our reputation and business could suffer harm as a result of counterfeit or unfit drugs sold under our brand name. In addition, thefts of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels, could adversely impact patient safety, our reputation and our business.

***Any lawsuits relating to infringement of intellectual property rights necessary to defend ourselves or enforce our rights will be costly and time consuming, and could be unsuccessful.***

Because competition in our industry is intense, competitors may infringe or otherwise violate our issued patents, patents of our licensors or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging, among other claims, that we infringe their patents. In addition, in a patent infringement proceeding there are many grounds upon which a party may assert invalidity or unenforceability of a patent, and a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. Litigation is uncertain and we cannot predict whether we would be successful in any such litigation. 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, managerial 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, managerial and other resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure.

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

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and/or 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 market price of our common stock. In some cases, we may choose not to pursue litigation against those that have infringed on our patents, or used them without authorization, due to the associated expenses and time commitment of monitoring these activities. If we fail to protect or to enforce our intellectual property rights successfully, our competitive position could suffer, which could harm our results of operations.

***We may not be successful in obtaining or maintaining necessary rights for our development pipeline through acquisitions and in-licenses.***

Presently we have rights to intellectual property to develop our product candidates, including patents and patent applications we own or exclusively license from the University of Texas at Austin. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

***If we are not able to prevent disclosure of our trade secrets and other proprietary information, the value of our technology and product candidates could be significantly diminished.***

We rely on trade secret protection to protect our interests in proprietary know-how and in processes that are unpatentable or for which patents are difficult to obtain or enforce. We may not be able to protect our trade secrets adequately. We have a policy of requiring our consultants, advisors and strategic partners to enter into confidentiality agreements and our employees to enter into invention, non-disclosure and non-compete agreements. However, no assurance can be given that we have entered into appropriate agreements with all parties that have had access to our trade secrets, know-how or other proprietary information, or that such agreements will provide for a meaningful protection of our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure of information. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and

time-consuming, and the outcome is unpredictable. Even if we are successful in prosecuting such claims, any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. Furthermore, although we seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems, it is also possible that our trade secrets, know-how or other proprietary information could be obtained by third parties as a result of breaches of such systems.

Any disclosure of confidential information into the public domain or to third parties could allow our competitors to learn our trade secrets and use the information in competition against us. In addition, others may independently discover or develop our trade secrets and proprietary information or substantially equivalent techniques. Any action to enforce our rights is likely to be time consuming and expensive, and may ultimately be unsuccessful, or may result in a remedy that is not commercially valuable. These risks are accentuated in foreign countries where laws or law enforcement practices may not protect proprietary rights as fully as in the United States or Europe. Any unauthorized disclosure of our trade secrets or confidential information could harm our competitive position.

***We may not be able to protect our intellectual property rights throughout the world.***

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and our patent rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly developing countries. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state 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.

As part of ordinary course prosecution and maintenance activities, we determine whether to seek patent protection outside the United States and in which countries. This also applies to patents we have acquired or in-licensed from third parties. In some cases, this means that we, or our predecessors in interest or licensors of patents within our portfolio, have sought patent protection in a limited number of countries for patents covering our product candidates. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and, even in jurisdictions where we have or are able to obtain issued patents, our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our 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. In addition, certain countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we may have limited remedies if our patents are infringed or if we are compelled to grant a license to our patents to a third party, which could materially diminish the value of those patents. In addition, there may be patent law reforms in foreign jurisdictions that could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents in those foreign jurisdictions. This could limit our potential revenue opportunities.

Accordingly, our efforts to obtain, register, and enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license. Moreover, patent protection must ultimately be sought 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.



***If we breach any of the agreements under which we license patent rights to use, develop and commercialize our product candidates or our technologies from third parties or, in certain cases, we fail to meet certain development deadlines, we could lose license rights that are important to our business.***

We are a party to license agreements under which we are granted rights to intellectual property that are important to our business and we expect that we may need to enter into additional license agreements in the future.

In December 2013, our wholly-owned subsidiaries AECASE, Inc. and AEMASE, Inc. each entered into an exclusive, worldwide license agreement, including the right to grant sublicenses, with the University of Texas at Austin for certain intellectual property owned by the University of Texas at Austin related to our program candidates under the AEB3103 and AEB2109 programs. In January 2017, we and the University of Texas at Austin entered into an Amended and Restated Patent License Agreement, or the Restated License, which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us. The Restated License was amended in August 2017, December 2017, and December 2018 to license additional patent applications, including our program candidates under the AEB4104 and AEB5100 programs. The intellectual property licensed under the Restated License includes an invention that was made with U.S. government support. The U.S. government therefore has certain rights in such inventions under the applicable funding agreements and under applicable law. In addition, we are subject to a requirement that the products covered by the applicable patents that are sold or used in the United States must be manufactured substantially in the United States unless a written waiver is obtained in advance from the U.S. government. The Restated License obligates us to make certain payments at the achievement of certain milestones and at regular intervals throughout the life of the license. The University of Texas at Austin may terminate the Restated License under certain circumstances, including for a breach by us that is not cured within 30 or 60 days of notice (depending on the type of breach), or if we or any of our affiliates or sublicensees participate in any proceeding to challenge the licensed patent rights (unless, with respect to sublicensees, we terminate the applicable sublicense).

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Any other licenses or other intellectual property agreements we may enter into may impose various diligence, milestone payment, royalty and other obligations on us. If disputes arise between us and our licensor or if we fail to comply with our obligations under current or future intellectual property agreements, potentially giving our counterparties the right to terminate these agreements, we might not be able to develop, manufacture or market any product that is covered by the agreement or face other penalties under the agreement. Such an occurrence could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

The loss of any one of our current licenses, or any other license we may acquire in the future, could prevent or impair our ability to successfully develop and commercialize the affected product candidates and thus materially harm our business, prospects, financial condition and results of operations.

***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, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology or product candidates, we may not be able to fully exercise or extract value from our intellectual property rights. The following examples are illustrative:

- others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of the patents that we own or license;
- we or our licensors or collaborators might not have been the first to make the inventions covered by an issued patent or pending patent application that we own or license;
- we or our licensors or collaborators might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing or misappropriating our intellectual property rights;
- pending patent applications that we own or license may not lead to issued patents;

- issued patents that we own or license may not provide us with any competitive advantages, or may be narrowly construed or held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Any of these events could significantly harm our business, results of operations and prospects.

***Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our products, and recent patent legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.***

As is the case with other biotechnology companies, our success is heavily dependent on patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted patent reform legislation. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this has created greater uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. 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.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The U.S. PTO has promulgated regulations and developed procedures to govern administration of the Leahy-Smith Act. The Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

The Leahy-Smith Act also requires an inventor to file a patent application on their invention prior to any other bona fide independent inventor. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to either (i) file any patent application related to our product candidates or (ii) invent any of the inventions claimed in our patents or patent applications.

The Leahy-Smith Act allows a third party to provide evidence in a U.S. PTO proceeding that could invalidate our patent claims. Accordingly, a third party may use the U.S. PTO procedures to invalidate our patent claims. In such an event, this circumstance could have a material adverse effect on our business.

***If we do not obtain patent term extensions under the Hatch-Waxman Act and similar legislation, thereby not extending the term of our marketing exclusivity for our product candidates, our business may be materially harmed.***

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one of the U.S. patents covering each of such approved product(s) or the use thereof may be eligible for up to five years of patent term restoration. Patent term extension allows a maximum of one patent to be extended per FDA-approved product. Patent term extension also may be available in certain foreign countries upon regulatory approval of our product candidates. Nevertheless, we may not be granted patent term extension either in the United States or in any foreign country because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the term of extension, as well as the scope of patent protection during any such extension, afforded by the governmental authority could be less than we request. In addition, if a patent we wish to extend is owned by another party and licensed to us, we may need to obtain approval and cooperation from our licensor to request the extension.

If we are unable to obtain patent term extension or restoration, or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

## Risks Related to Our Common Stock

***Our executive officers, directors and principal stockholders, if they choose to act together, will continue to have the ability to control all matters submitted to stockholders for approval.***

We have a concentrated stockholder base and our executive officers and directors, combined with our stockholders who, to our knowledge, each owned more than 5% of our outstanding common stock, in the aggregate, beneficially own shares representing a substantial number of our capital stock as of December 31, 2019. As a result, if these stockholders were to choose to act together, they may be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire or may result in you obtaining a premium for your shares.

***Our internal control over financial reporting does not currently meet the standards required by Section 404 of the Sarbanes-Oxley Act, and failure to achieve and maintain effective internal control over financial reporting in accordance with Section 404 of the Sarbanes-Oxley Act could have a material adverse effect on our business and stock price.***

Pursuant to Section 404, we have been required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles in the United States. We may encounter problems or delays in implementing any changes necessary to make a favorable assessment of our internal control over financial reporting. If we cannot favorably assess the effectiveness of our internal control over financial reporting, or if our independent registered public accounting firm is unable to provide an unqualified attestation report on our internal controls when required, investors could lose confidence in our financial information and the price of our common stock could decline.

Additionally, the existence of any material weakness or significant deficiency would require management to devote significant time and incur significant expense to remediate any such material weaknesses or significant deficiencies and management may not be able to remediate any such material weaknesses or significant deficiencies in a timely manner. The existence of any material weakness in our internal control over financial reporting could also result in errors in our financial statements that could require us to restate our financial statements causing us to fail to meet our reporting obligations and cause stockholders to lose confidence in our reported financial information, all of which could materially and adversely affect us.

***Provisions in our corporate charter documents and under Delaware law could make an acquisition of our company, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.***

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least two-thirds of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws.

Moreover, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

Any of these provisions of our charter documents or Delaware law could, under certain circumstances, depress the market price of our common stock.

***Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders’ ability to obtain a favorable judicial forum for disputes with us or our directors, officers, employees or agents.***

Our amended and restated certificate of incorporation provides that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or agents to us or our stockholders, any action asserting a claim arising pursuant to any provision of the DGCL, our amended and restated certificate of incorporation or our amended and restated bylaws or any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein and the claim not being one which is vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery or for which the Court of Chancery does not have subject matter jurisdiction. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our amended and restated certificate of incorporation. This choice of forum provision may limit our stockholders’ ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, employees or agents, which may discourage such lawsuits against us and our directors, officers, employees and agents even though an action, if successful, might benefit our stockholders. Stockholders who do bring a claim in the Court of Chancery could face additional litigation costs in pursuing any such claim, particularly if they do not reside in or near Delaware. The Court of Chancery may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments or results may be more favorable to us than to our stockholders. Alternatively, if a court were to find this provision 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 have a material adverse effect on our business, financial condition or results of operations.

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

Our stock price is volatile. The stock market in general and the market for smaller biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- the success or failure of competitive products or technologies;
- results of ongoing or planned clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;

- operating results that fail to meet expectations of securities analysts that cover our company;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic and market conditions; and
- the other factors described in this “Risk Factors” section.

***We may be subject to securities litigation, which is expensive and could divert management attention.***

Our stock price is volatile, and in the past companies that have experienced volatility in the market price of their stock have been subject to an increased incidence of securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management’s attention from other business concerns, which could seriously harm our business.

If securities or industry analysts do not publish research or reports about our business, or publish negative reports about our business, our stock price and trading volume could decline.

The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us or provide favorable coverage. If one or more of the analysts who cover us downgrade our stock or change their opinion of our stock, our stock price would likely decline. If one or more of these analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our stock price or trading volume to decline.

***We have broad discretion in the use of the net proceeds from our public offerings and may not use them effectively.***

Our management has broad discretion in the application of the net proceeds from our public offerings, and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Our management could spend the net proceeds from our public offerings in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from our public offerings in a manner that does not produce income or that loses value.

***Future sales of our common stock in the public market could cause the market price of our common stock to drop significantly, even if our business is doing well.***

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock and make it more difficult for you to sell your common stock at a time and price that you deem appropriate.

Certain holders of our common stock have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in Securities Act registration statements that we may file for ourselves or other stockholders. Once we register these shares, they can be freely sold in the public market. Moreover, we have also registered under the Securities Act shares of common stock that we may issue under our equity compensation plans.

In addition, on February 13, 2019, our shelf registration statement on Form S-3 for the potential offering, issuance and sale by us of up to \$200.0 million of our common stock, preferred stock, debt securities, warrants to purchase our common stock, preferred stock and debt securities, subscription rights to purchase our common stock, preferred stock and debt securities, and units consisting of all or some of these securities was declared effective by the SEC. In connection with this shelf registration statement, we have entered into an “at-the-market” offering of our common stock pursuant to a sales agreement between us and Jefferies LLC, or Jefferies. Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to Jefferies at any time throughout the term of the sales agreement, which has a term equal to the term of the registration statement on Form S-3 unless otherwise terminated earlier by us or Jefferies pursuant to the terms of the sales agreement. The number of shares that are sold by Jefferies after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with Jefferies. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued. Issuances of any shares sold pursuant to the sales agreement will have a dilutive effect on our existing stockholders. Further, if we sell common stock, preferred stock, convertible securities and other equity securities in other transactions pursuant to our shelf registration statement on Form S-3, existing investors may be materially diluted by such subsequent sales and new investors could gain rights superior to our existing stockholders.

In addition, in the future, we may issue additional shares of common stock or other equity or debt securities convertible into common stock in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise, including upon exercise of our pre-funded warrants. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline.

***There is no public market for our pre-funded warrants.***

There is no public trading market for our pre-funded warrants issued in the February 2019 public offering, and we do not expect a market to develop. In addition, we do not intend to apply to list the pre-funded warrants on any securities exchange or nationally recognized trading system, including the Nasdaq Global Market. Without an active market, the liquidity of the pre-funded warrants will be limited and their value may be adversely impacted.

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

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company through December 31, 2021. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting of Section 404(b) of the Sarbanes-Oxley Act;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

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

***We will continue to incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.***

As a public company, and particularly after we are no longer an emerging growth company, we incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain and maintain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. As discussed above, if we cease to be an emerging growth company, we will be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm as required by Section 404(b). To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

***Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.***

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an “ownership change,” generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change income or taxes may be limited. It is possible that we may have triggered an “ownership change” limitation. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership (some of which are outside of our control). As a result, if we earn net taxable income, our ability to use our pre-change NOLs and other pre-change tax attributes to offset U.S. federal taxable income or taxes may be subject to limitations, which could potentially result in increased future tax liability to us. Our NOLs and other tax attributes arising before our conversion from a Delaware limited liability company to a Delaware corporation in 2015 also may be limited by the Separate Return Limitation Year rule, which could increase our U.S. federal tax liability. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

***Since we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, stock price appreciation, if any, will be your sole source of gain.***

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

**ITEM 1B. UNRESOLVED STAFF COMMENTS**

None.

**ITEM 2. PROPERTIES**

In April 2019, we entered into a lease agreement (the “Las Cimas Lease”) for corporate headquarters and laboratory space located in Austin, Texas. The Las Cimas Lease includes approximately 30,000 square feet and commenced on April 30, 2019, with an expiration date of April 30, 2028. Moreover, we lease approximately 10,100 and 4,560 square feet of additional office and laboratory space, respectively, in Austin, Texas. The leases for the additional office and laboratory space will expire in December 2020 and September 2021, respectively. We intend to lease additional space if we add employees and expand geographically. We believe that our facilities are adequate to meet our needs for the immediate future, and that, should it be needed, suitable additional space will be available on commercially reasonable terms to accommodate any such expansion of our operations.

**ITEM 3. LEGAL PROCEEDINGS**

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. Regardless of outcome, litigation can have an adverse impact on us due to defense and settlement costs, diversion of management resources, negative publicity and reputational harm, 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

#### Market Information and Holders

Our common stock is traded on The Nasdaq Global Market under the symbol "AGLE."

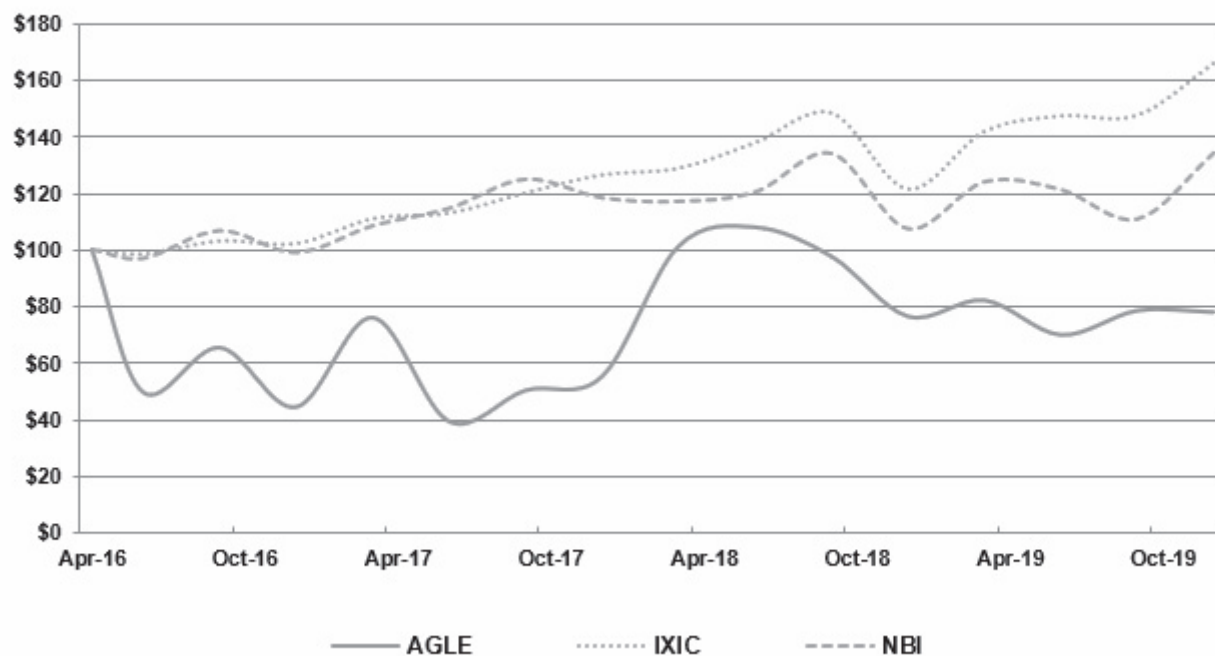
As of February 20, 2020, there were approximately 24 stockholders of record of our common stock based on information provided by our transfer agent. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

#### Stock Price Performance Graph

This graph shall not be deemed "soliciting material" or be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities under that Section, and shall not be deemed to be incorporated by reference into any of our filings under the Securities Act whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

The following stock performance graph compares our total stock return with the total return for (i) the Nasdaq Composite Index and the (ii) the Nasdaq Biotechnology Index for the period from April 7, 2016 (the date our common stock commenced trading on the Nasdaq Global Market) through December 31, 2019. The figures represented below assume an investment of \$100 in our common stock at the closing price of \$9.77 on April 7, 2016 and in the Nasdaq Composite Index and the Nasdaq Biotechnology Index on April 7, 2016 and the reinvestment of dividends into shares of common stock. The comparisons in the table are required by the SEC and are not intended to forecast or be indicative of possible future performance of our common stock.

**Comparison of Cumulative Return**





\$100 investment in stock or index	Ticker	April 7, 2016	December 31, 2016	December 31, 2017	December 31, 2018	December 31, 2019
Aeglea Biotherapeutics, Inc.	AGLE	\$ 100.00	\$ 44.52	\$ 55.37	\$ 76.66	\$ 78.20
Nasdaq Composite Index	IXIC	\$ 100.00	\$ 102.12	\$ 126.43	\$ 121.42	\$ 165.98
Nasdaq Biotechnology Index	NBI	\$ 100.00	\$ 98.88	\$ 118.33	\$ 107.34	\$ 134.30

## Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future.

## Securities Authorized for Issuance under Equity Compensation Plans

The information required by this item will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Regulation 14A.

## Recent Sales of Unregistered Securities

None.

## Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

## ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The consolidated statements of operations data for the years ended December 31, 2019, 2018, and 2017, and the balance sheet data as of December 31, 2019 and 2018 are derived from our audited financial statements included elsewhere in this Annual Report on Form 10-K. The selected consolidated statements of operations data for the year ended December 31, 2016 and 2015 and the balance sheet data as of December 31, 2017, 2016, and 2015 is derived from our audited financial statements which are not included in this Annual Report on Form 10-K.

Our historical results are not necessarily indicative of the results to be expected in the future. You should read the selected financial data below in conjunction with the section of this report entitled “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and the related notes included in this Annual Report on Form 10-K.

	Year Ended December 31,				
	2019	2018	2017	2016	2015
(in thousands, except share and per share amounts)					
<b>Consolidated Statements of Operations Data:</b>					
Revenues:					
Grant	\$ —	\$ 3,888	\$ 5,205	\$ 4,628	\$ 6,085
Operating expenses:					
Research and development	64,600	36,719	22,815	18,143	11,453
General and administrative	15,734	12,632	10,066	8,391	5,947
Total operating expenses	80,334	49,351	32,881	26,534	17,400
Loss from operations	(80,334)	(45,463)	(27,676)	(21,906)	(11,315)
Other income (expense):					
Interest income	2,143	1,172	482	244	22
Other expense, net	(63)	(57)	(42)	(36)	(2)
Total other income	2,080	1,115	440	208	20
Net loss	(78,254)	(44,348)	(27,236)	(21,698)	(11,295)
Deemed dividend to convertible preferred stockholders	—	—	—	—	(228)
Net loss attributable to common shareholders and stockholders	<u>\$ (78,254)</u>	<u>\$ (44,348)</u>	<u>\$ (27,236)</u>	<u>\$ (21,698)</u>	<u>\$ (11,523)</u>
Common Stock:					
Net loss per share, basic and diluted	\$ (2.45)	\$ (2.13)	\$ (1.80)	\$ (2.22)	\$ (19.21)
Net loss attributable to common stockholders	\$ (78,254)	\$ (44,348)	\$ (27,236)	\$ (21,698)	\$ (11,523)
Weighted-average common shares outstanding, basic and diluted	31,949,633	20,822,560	15,128,192	9,791,728	599,788

	As of December 31,				
	2019	2018	2017	2016	2015
(in thousands)					
<b>Consolidated Balance Sheet Data:</b>					
Cash, cash equivalents, marketable securities, and restricted cash	\$ 73,449	\$ 74,513	\$ 50,299	\$ 63,502	\$ 33,062
Working capital	56,146	66,432	49,362	62,459	35,763
Total assets	83,183	77,739	56,077	67,063	38,654
Total liabilities	23,102	10,311	5,740	4,097	2,550
Convertible preferred shares	—	—	—	—	58,311
Accumulated deficit	(195,115)	(116,861)	(72,513)	(45,277)	(23,579)
Total stockholders’ equity (deficit)	60,081	67,428	50,337	62,966	(22,207)

## ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

*You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes appearing in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. As used in this report, unless the context suggests otherwise, "we," "us," "our," "the Company" or "Aeglea" refer to Aeglea BioTherapeutics, Inc.*

### Overview

We are a clinical-stage biotechnology company developing next-generation human enzyme therapeutics as disruptive solutions for rare and other high-burden diseases. We believe our expertise in enzyme medicine, advanced bioengineering technology and focused approach enables us to identify and pursue opportunities to address important unmet medical needs for patient communities with few options.

We employ a distinctive, replicable platform to fuel our innovative pipeline, which we believe reduces key risks throughout the development process and provides a greater likelihood of clinical success and commercial adoption.

We are driven by the urgent needs of patient communities who have inadequate or no therapeutic options available to address these debilitating diseases. Our purpose-driven and patient focused approach to the selection and development of novel assets into clinical evaluation is guided by defined strategic considerations:

- Clear, urgent unmet medical need
- Rigorous preclinical data and strong scientific rationale
- Mechanistic opportunity to create or enhance enzymatic activity through novel engineering
- Meaningful and sustainable commercial opportunities
- Potential to be first in class or best in class, with little competition

Our lead product candidate, pegzilarginase, is engineered to degrade the amino acid arginine and is being developed to lower arginine levels in patients with Arginase 1 Deficiency, a rare genetic progressive disease, presenting in early childhood that results in severe complications and early mortality. Pegzilarginase is currently being evaluated in a global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial and in a Phase 2 open-label extension study for patients with Arginase 1 Deficiency. Additionally, we announced the filing of a Clinical Trial Application with the United Kingdom's Medicines and Healthcare Products Regulatory Agency for ACN00177, a novel engineered human enzyme therapy designed to treat Homocystinuria, a serious metabolic disorder that results in elevated levels of plasma homocysteine. We are also building a pipeline of additional product candidates targeting key amino acids and metabolites, including AEB5100 for the treatment of cystinuria

Since inception, we have devoted substantially all of our efforts and resources to identifying and developing product candidates, conducting nonclinical studies, initiating and conducting clinical trials, recruiting personnel and raising capital. To date, we have financed our operations primarily through private placements of our preferred stock, the initial public offering of our common stock, follow-on public offerings of our common stock, and collection of a research grant.

We have incurred net losses in each year since inception. Our net losses were \$78.3 million, \$44.3 million, and \$27.2 million for the years ended December 31, 2019, 2018, and 2017, respectively, and have resulted from costs incurred in connection with our research and development programs and from general and administrative expenses associated with our operations. As of December 31, 2019, we had an accumulated deficit of \$195.1 million. We expect to continue to incur operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and from year to year. We anticipate that our expenses will increase significantly as we continue our clinical development activities for our product candidates and prepare for the potential commercialization of our lead product candidate, pegzilarginase; concurrently develop our pipeline product candidates, including a planned Phase 1/2 clinical trial for Homocystinuria in the second quarter of 2020; expand and protect our intellectual property portfolio; hire additional personnel; and continue to operate as a public company.

## Components of Operating Results

### Revenue

To date, we recognized revenue solely from a research grant from the Cancer Prevention and Research Institute of Texas, or CPRIT, and have not generated any revenue from the sale of any of our product candidates. Our ability to generate product revenues, which we do not expect will occur for several years, if ever, will depend heavily on the successful development, regulatory approval, and eventual commercialization of our product candidates.

In June 2015, we entered into a grant agreement with CPRIT, or the Grant Contract, for \$19.8 million for use in developing cancer treatments by exploiting the metabolism of cancer cells. The Grant Contract covered a four-year period from June 1, 2014 through May 31, 2018. The grant allowed us to receive funds in advance of costs and allowable expenses being incurred. We recorded the revenue as qualifying costs were incurred and there was reasonable assurance that the conditions of the award had been met for collection. Proceeds received prior to the costs being incurred or the conditions of the award being met were recognized as deferred revenue until the services were performed and the conditions of the award were met.

On a quarterly basis, we were required to submit a financial reporting package outlining the nature and extent of reimbursable costs paid and requesting reimbursement under the grant. At the end of each period, qualifying costs paid prior to reimbursement resulted in the recognition of a grant receivable. As of December 31, 2018, we collected the full \$19.8 million grant proceeds and will not be recognizing grant revenue under the contract in future periods.

### Research and development expenses

Research and development expenses consist primarily of costs incurred for the discovery and development of our product candidates, including, our lead product candidate, pegzilarginase, and ACN00177. In addition to operating an internal research laboratory, we contract with external providers for nonclinical studies and clinical trials. Our research and development expenses include:

- costs from acquiring clinical trial materials and services performed for contracted services with contract manufacturing organizations;
- fees paid to clinical trial sites, clinical research organizations, contract research organizations, contract manufacturing organizations, nonclinical research companies, and academic institutions; and
- employee and consultant-related expenses incurred, which include salaries, benefits, travel and stock-based compensation.

Research and development costs are expensed as incurred. Advance payments for goods or services to be rendered in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Research and development expenses have historically represented the largest component of our total operating expenses. We plan to increase our research and development expenses for the foreseeable future as we continue the development of our product candidates.

Our expenditures on current and future nonclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion. The duration, costs, and timing of clinical trials and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, and expenses of our ongoing research activities as well as any additional clinical trials and other research and development activities;
- future clinical trial results;
- uncertainties in clinical trial enrollment rates or drop-out or discontinuation rates of patients;
- changes in the competitive drug development environment;
- potential safety monitoring or other studies requested by regulatory agencies;
- significant and changing government regulation; and
- the timing and receipt of regulatory approvals, if any.

The process of conducting the necessary clinical research to obtain FDA and other regulatory approval is costly and time consuming and the successful development of our product candidates is highly uncertain. The risks and uncertainties associated with our research and development projects are discussed more fully in Part I, Item 1A of this Annual Report titled "Risk Factors." As a result of these risks and uncertainties, we are unable to determine with any degree of certainty the duration and completion costs of our research and development projects, or if, when, or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

### ***General and administrative expenses***

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, commercial development, operations, and human resources functions. Other significant costs include legal fees relating to corporate matters and fees for insurance, accounting, consulting, facilities, and recruiting services.

We expect that our general and administrative expenses will increase in the future to support our continued research and development activities, and the potential commercialization of our product candidates. These increases will likely include higher costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses. Additionally, we have incurred and expect to continue to incur increased costs associated with being a public company, including expenses related to services associated with maintaining compliance with Nasdaq listing rules and SEC requirements, insurance, and investor relations costs.

### ***Interest income***

Interest income consists of interest earned on our cash, cash equivalents, marketable securities, and restricted cash.

### ***Income taxes***

We serve as a holding company for our seven wholly-owned U.S. subsidiary corporations and file a consolidated corporate federal income tax return. We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to our lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

We recognize benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. Our policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense.

### **Critical Accounting Policies and Estimates**

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and related disclosures. These estimates form the basis for judgments we make about the carrying values of our assets and liabilities, which are not readily apparent from other sources. We base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. On an ongoing basis, we evaluate our estimates and assumptions. Our actual results may differ materially from these estimates under different assumptions or conditions.

Our critical accounting policies are those policies which require the most significant judgments and estimates in the preparation of our consolidated financial statements. We believe that the assumptions and estimates associated with our most critical accounting policies are those relating to accrued research and development costs.

We define our critical accounting policies as those accounting principles generally accepted in the United States that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations, as well as the specific manner in which we apply those principles. Our significant accounting policies are more fully described in Note 2 to our audited consolidated financial statements appearing elsewhere in this annual report.

## Accrued research and development costs

We record the costs associated with research nonclinical studies, clinical trials, and manufacturing development as incurred. These costs are a significant component of our research and development expenses, with a substantial portion of our on-going research and development activities conducted by third-party service providers, including contract research organizations, or CROs, and contract manufacturing organizations, or CMOs.

We accrue for expenses resulting from obligations under agreements with CROs, CMOs, and other outside service providers for which payment flows do not match the periods over which materials or services are provided to us. We record accruals based on estimates of services received and efforts expended pursuant to agreements established with CROs, CMOs, and other outside service providers. These estimates are typically based on contracted amounts applied to the proportion of work performed and determined through analysis with internal personnel and external service providers as to the progress or stage of completion of the services. We make significant judgments and estimates in determining the accrual balance in each reporting period. In the event advance payments are made to a CRO, CMO, or outside service provider, the payments will be recorded as a prepaid asset which will be amortized as the contracted services are performed. As actual costs become known, we adjust our accruals. Inputs, such as the services performed, the number of patients enrolled, or the study duration, may vary from our estimates, resulting in adjustments to research and development expense in future periods. Changes in these estimates that result in material changes to our accruals could materially affect our results of operations.

## Results of Operations

### Comparison of the Years Ended December 31, 2019 and 2018

A discussion and analysis of our financial condition and results of operations for the year ended December 31, 2017 is included in Item 7 of Part II, "Management's Discussion and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the year ended December 31, 2018 filed with the SEC on March 7, 2019.

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Dollar Change	% Change
	2019	2018		
	(dollars in thousands)			
Revenues:				
Grant	\$ —	\$ 3,888	\$ (3,888)	100%
Operating expenses:				
Research and development	64,600	36,719	27,881	76%
General and administrative	15,734	12,632	3,102	25%
Total operating expenses	80,334	49,351	30,983	63%
Loss from operations	(80,334)	(45,463)	(34,871)	77%
Interest income	2,143	1,172	971	83%
Other expense	(63)	(57)	(6)	11%
Net loss	<u>\$ (78,254)</u>	<u>\$ (44,348)</u>	<u>\$ (33,906)</u>	76%

**Grant Revenues.** There was no grant revenue recognized for the year ended December 31, 2019, resulting in a \$3.9 million decrease, or 100%, from \$3.9 million for the year ended December 31, 2018. The grant contract ended in May 2018 with the full \$19.8 million grant recognized as revenue over the life of the award.

**Research and Development Expenses.** Research and development expenses increased by \$27.9 million, or 76%, to \$64.6 million for the year ended December 31, 2019 from \$36.7 million for the year ended December 31, 2018. The change in research and development expenses was primarily due to:

- Higher manufacturing expenses, which increased by \$18.2 million as a result of accelerated investment in manufacturing and pre-commercial activities for pegzilarginase and a ramp-up in manufacturing activities for ACN00177 in Homocystinuria;

- Higher clinical development expenses, which increased by \$3.8 million as a result of initiating our global pivotal Phase 3 PEACE trial for pegzilarginase in patients with Arginase 1 Deficiency, advancing and exceeding enrollment of our Phase 2 open-label extension study for pegzilarginase in patients with Arginase 1 Deficiency, and advancing and concluding enrollment of our Phase 1/2 combination trial in patients with small cell lung cancer;
- Higher nonclinical expenses, which increased by \$2.2 million as a result of advancing our toxicology and IND-enabling studies to support continued clinical development of our Homocystinuria program and expanding our internal laboratory capabilities; and
- Higher personnel-related expenses, which increased by \$3.5 million as a result of additional employee headcount to expand our manufacturing and clinical development capabilities along with our internal research laboratory team.

*General and Administrative Expenses.* General and administrative expenses increased by \$3.1 million, or 25%, to \$15.7 million for the year ended December 31, 2019 from \$12.6 million for the year ended December 31, 2018. The increase in general and administrative expenses was primarily due to additional employee headcount, compensation, and office space to support company growth. Increases in non-cash stock compensation expense accounted for \$0.4 million of the increase.

*Interest Income.* The increase in interest income to \$2.1 million for the year ended December 31, 2019 from \$1.2 million for the year ended December 31, 2018 was primarily due to investment diversification and the investment of additional funds received as a result of our public offerings in February 2019.

## **Liquidity and Capital Resources**

### **Sources of liquidity**

We are a clinical-stage biotechnology company with a limited operating history, and due to our significant research and development expenditures, we have generated operating losses since our inception and have not generated any revenue from the sale of any products. Since our inception and through December 31, 2019, we have funded our operations primarily by raising an aggregate of \$273.5 million of gross proceeds from the sale and issuance of convertible preferred and common equity securities, pre-funded stock warrants, and the collection of grant proceeds.

In February 2019, we sold an aggregate of 4,625,000 shares of common stock at a public offering price of \$8.00 per share and pre-funded warrants to purchase up to 4,000,000 shares of common stock at a public offering price of \$7.9999 per warrant. This includes the full exercise by the underwriters of their option to purchase up to 1,125,000 additional shares of common stock. The gross proceeds from this public offering were \$69.0 million, resulting in net proceeds of \$64.5 million after deducting underwriting discounts and commissions and offering costs. Additionally, we filed a new shelf registration statement on Form S-3 that was declared effective in February 2019 by the SEC for the potential offering, issuance and sale by us of up to \$200.0 million, or the 2019 Registration Statement, of our common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock and debt securities, subscription rights to purchase common stock and units consisting of all or some of these securities.

In December 2018, we entered into a sales agreement, or the 2018 Sales Agreement, with Jefferies LLC, as sales agent, to issue and sell shares of our common stock for an aggregate offering price of \$60.0 million under an at-the-market offering program pursuant to the 2019 Registration Statement. As of December 31, 2019, all \$60.0 million of our common stock remain available for sale pursuant to the 2018 Sales Agreement.

The 2019 Registration Statement and 2018 ATM program replaced the 2017 shelf registration statement on Form S-3 (2017 Registration Statement) and sales agreement with JonesTrading Institutional Services LLC (2017 ATM), as sales agent and underwriter, we filed with the SEC in May 2017.

During the year ended December 31, 2018, we sold an aggregate of:

- 5,046,510 shares of common stock in an underwritten public offering pursuant to the 2017 Registration Statement for gross proceeds of \$40.4 million, resulting in net proceeds of \$37.7 million after deducting underwriting discounts and commissions and offering expenses and
- 1,845,820 shares of common stock in a single transaction pursuant to the 2017 ATM for net proceeds of \$16.4 million.

During the year ended December 31, 2017, we sold an aggregate of 3,000,000 shares of common stock in an underwritten public offering pursuant to the 2017 Registration Statement for gross proceeds of \$12.3 million, resulting in net proceeds of \$11.4 million after deducting underwriting discounts and commissions and offering expenses.

In June 2015, we entered into the Grant Contract with CPRIT, under which CPRIT agreed to provide up to \$19.8 million in grant funding to fund our development of pegzilarginase. Through December 31, 2018, we have collected the full \$19.8 million in grant proceeds under the grant contract. For a detailed discussion of this grant, see “Business—Grant Agreement.”

Our primary use of cash is to fund the development of our product candidates, prepare for the potential commercialization of our lead product candidate, pegzilarginase and advance our pipeline. This includes both the research and development costs and the general and administrative expenses required to support those operations. Since we are a clinical-stage biotechnology company, we have incurred significant operating losses since our inception and we anticipate such losses, in absolute dollar terms, to increase as we continue clinical development of our product candidates, prepare for the potential commercialization of pegzilarginase, and expand our development efforts in our pipeline of nonclinical candidates.

### **Future funding requirements and operational plan**

Our operational plan for the near future is to continue clinical trials for our lead product candidate pegzilarginase in Arginase 1 Deficiency and our ACN00177 product candidate for the treatment of Homocystinuria, prepare for the potential commercialization of pegzilarginase, and to advance development activities for our AEB5100 program for Cystinuria. As such, we plan to increase our research and development expenditures and general and administrative expenditures with nonclinical studies, clinical trials, manufacturing, and commercial development. We expect our principal expenditures during this time period to include expenses for the following:

- funding the continuing development of pegzilarginase and ACN00177;
- funding the advancement of additional product candidates; and
- funding working capital, including general operating expenses.

Due to our significant research and development expenditures, we have generated substantial losses in each period since inception. We have an accumulated deficit of \$195.1 million as of December 31, 2019. We anticipate that we will continue to generate as we develop our product candidates, seek regulatory approval of those candidates and begin to commercialize any approved products. Until such time as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity or debt financings, research grants, collaborations, or other sources. We currently have no debt, credit facility or additional committed capital. To the extent that we raise additional equity, the ownership interest of our stockholders will be diluted.

Based on our available cash, cash equivalents, marketable securities, and restricted cash of \$73.4 million as of December 31, 2019, we believe that we have sufficient resources to fund our operations through the first quarter of 2021. We have based this estimate on assumptions that may prove to be incorrect, however, and we could deplete our capital resources sooner than we expect.

### **Cash flows**

A discussion and analysis of our financial condition and cash flows for the year ended December 31, 2017 is included in Item 7 of Part II, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2018 filed with the SEC on March 7, 2019.

The following table summarizes our cash flows for the periods indicated (in thousands):

	<u>Year Ended December 31,</u>	
	<u>2019</u>	<u>2018</u>
Net cash and cash equivalents (used in) provided by:		
Operating activities	\$ (65,692)	\$ (32,193)
Investing activities	(1,739)	(15,231)
Financing activities	65,723	57,068
Net increase (decrease) in cash and cash equivalents	<u>\$ (1,708)</u>	<u>\$ 9,644</u>



### *Cash used in operating activities*

Cash used in operating activities for the year ended December 31, 2019 was \$65.7 million and reflected a net loss of \$78.3 million. The cash impact of our net loss was offset by non-cash expenses of \$4.9 million for stock-based compensation, \$0.5 million for operating lease expense, \$0.4 million for depreciation and amortization, and \$0.3 million for the net accretion of discounts on marketable securities exceeding the purchased discounts for the period. The net change in operating assets and liabilities of \$7.1 million was related to a \$7.7 million increase in accounts payable and accrued liabilities due to additional research and development costs associated with the clinical trials and manufacturing activities for pegzilarginase in patients with Arginase 1 Deficiency, which was partially offset by a \$0.3 million increase in prepaid expenses and other assets due to advanced payments associated with our on-going clinical trials to treat Arginase 1 Deficiency and a \$0.3 million decrease in operating lease liabilities.

Cash used in operating activities for the year ended December 31, 2018 was \$32.2 million and reflected a net loss of \$44.3 million. The cash impact of our net loss was offset by non-cash expenses of \$4.3 million for stock-based compensation, \$0.3 million for net discount purchases and accretion on marketable securities, and \$0.3 million for depreciation and amortization. The change in operating assets and liabilities of \$7.2 million was primarily related to a \$4.2 million increase in accrued and other liabilities due to additional research and development costs associated with the clinical trials for pegzilarginase in patients with Arginase 1 Deficiency and cancer, as well as a \$3.1 million decrease in grants accounts receivable due to concluding the grant contract and collecting the remaining proceeds.

### *Cash used in investing activities*

Cash used in investing activities for the year ended December 31, 2019 was \$1.7 million and consisted of \$91.9 million in purchases of marketable securities and \$1.5 million in purchases of property and equipment offset by \$91.7 million in maturities and sales of marketable securities.

Cash used in investing activities for the year ended December 31, 2018 was \$15.2 million and consisted of \$62.2 million in purchases of marketable securities and \$0.4 million in purchases of property and equipment offset by \$47.4 million in maturities of marketable securities.

### *Cash provided by financing activities*

Cash provided by financing activities for the year ended December 31, 2019 was \$65.7 million, which consisted of \$69.0 million from the public offerings of our common stock in February 2019, offset by \$4.1 million in underwriting discounts and commissions and \$0.6 million in paid offering costs related to the offering and 2019 Registration Statement, and \$1.4 million in proceeds received from stock option exercises and sale of common stock under our 2016 Employee Stock Purchase Plan.

Cash provided by financing activities for the year ended December 31, 2018 was \$57.1 million, which consisted of \$57.4 million from the public offerings of our common stock, offset by \$2.9 million in underwriting discounts and commissions and \$0.4 million in offering costs, and \$3.0 million in proceeds received from stock option exercises and sale of common stock under our 2016 Employee Stock Purchase Plan.

## **Contractual Obligations**

The following table summarizes our contractual obligations as of December 31, 2019 (in thousands):

	Payments Due by Period				Total
	Less than 1 year	1 to 3 years	4 to 5 years	More than 5 years	
Operating leases	\$ 1,167	\$ 2,068	\$ 2,106	\$ 3,796	\$ 9,137
Finance lease	32	32	—	—	64
Total	\$ 1,199	\$ 2,100	\$ 2,106	\$ 3,796	\$ 9,201

We have entered into agreements in the normal course of business with contract research organizations for clinical trials and contract manufacturing organizations, and with vendors for preclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon 30 to 60 days' prior written notice to the vendor.

## **Contingent contractual obligations**

The terms of the Grant Contract require that we pay CPRIT tiered royalties in the low- to mid-single digit percentages on revenues from sales and license of products or services that are based upon, utilize, are developed from or materially incorporate the intellectual property resulting from the grant-funded activities for pegzilarginase. Such royalties reduce to less than one percent after a mid-single digit multiple of the grant funds have been repaid to CPRIT in royalties. Such royalties are payable for so long as we have marketing exclusivity or patents covering the applicable product or service (or twelve years from commercial sale of product or service in certain countries if there is no such exclusivity or patent protection).

On December 24, 2013, two of our wholly owned subsidiaries, AECCase, Inc., or AECCase, and AEMase, Inc., or AEMase, entered into license agreements with the University under which the University granted to AECCase and AEMase exclusive, worldwide, sublicenseable licenses. The University granted to AECCase a license under a patent application relating to the right to use technology related to our AEB3103 product candidate. The University granted to AEMase a license under a patent relating to the right to use technology related to our AEB2109 product candidate. On January 31, 2017, we entered into an Amended and Restated Patent License Agreement, or the Restated License, with the University which consolidated the two license agreements dated December 24, 2013, revised certain obligations, and licensed additional patent applications and invention disclosures to Aeglea. In December 2017, the Restated License was further amended to revise certain diligence milestones.

With respect to each product candidate covered by the Restated License, we could be required to pay the University up to \$6.4 million in milestone payments based on the achievement of certain development milestones, including clinical trials and regulatory approvals, the majority of which are due upon the achievement of later development milestones, including a \$5.0 million payment due on regulatory approval of a product and a \$0.5 million payment payable on final regulatory approval of a product for a second indication. In addition, we are required to pay the University a low single digit royalty on worldwide-net sales of products covered under the Restated License, together with a revenue share on non-royalty consideration received from sublicensees. The rate of the revenue share ranges from 6.5% to 25% depending on the date the sublicense agreement is signed. The University may terminate the agreement under certain circumstances, including for a breach by us that is not cured within 30 or 60 days of notice (depending on the type of breach), or if we or any of our affiliates or sublicensees participate in any proceeding to challenge the licensed patent rights (unless, with respect to sublicensees, we terminate the applicable sublicense).

## **Off Balance Sheet Arrangements**

Through December 31, 2019, we do not have any off-balance sheet arrangements, as defined by applicable SEC regulations.

## **JOBS Act Accounting Election**

We are an “emerging growth company,” as defined in the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards, and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

## **Recent Accounting Pronouncements**

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), which establishes a comprehensive new lease accounting model. The new standard: (a) clarifies the definition of a lease; (b) requires a dual approach to lease classification similar to current lease classifications; and (c) causes lessees to recognize leases on the balance sheet as a lease liability with a corresponding right-of-use (ROU) asset. On January 1, 2019, we adopted Topic 842 using the modified retrospective approach as of the adoption date in accordance with ASU No. 2018-11, Leases (Topic 842): Targeted Improvements. Results for the year ended December 31, 2019 are presented under Topic 842. No prior period amounts were adjusted and continue to be reported in accordance with previous lease guidance, ASC Topic 840, Leases. We elected all of the available practical expedients permitted under the transition guidance within the new standard, which among other things, allowed us to carry forward the historical lease classification of those leases in place as of January 1, 2019.

The following table summarizes the impact of the adoption of Topic 842 on the accompanying balance sheet as of January 1, 2019 (in thousands):

	December 31, 2018	Effect of the Adoption of Topic 842	January 1, 2019
Other non-current assets <sup>(1)</sup>	\$ 50	\$ 691	\$ 741
<b>Lease Liabilities:</b>			
Current operating lease liabilities	\$ —	\$ 339	\$ 339
Non-current operating lease liabilities	\$ —	\$ 465	\$ 465
Accrued and other current liabilities <sup>(2)</sup>	\$ 9,576	\$ (41)	\$ 9,535
Other non-current liabilities <sup>(3)</sup>	\$ 72	\$ (72)	\$ —

(1) Operating lease right-of-use assets are classified within other non-current assets.

(2) Current deferred rent was classified within accrued and other current liabilities as of December 31, 2018.

(3) Non-current deferred rent was classified within other non-current liabilities as of December 31, 2018.

The adjustments due to the adoption of Topic 842 related to the recognition of operating lease right-of-use assets and lease liabilities for the existing operating leases. A cumulative-effect adjustment to the beginning accumulated deficit balance was not required.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments-Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*, which changes the impairment model for most financial assets and certain other instruments. For available-for-sale debt securities with unrealized credit losses, the credit losses will be recognized as allowances rather than as reductions in the amortized cost of the securities. The guidance is effective for interim and annual periods beginning after December 15, 2019. The guidance and its amendments will be applied using a modified retrospective approach with the cumulative effect recognized as an adjustment to retained earnings. We do not expect the adoption of ASU 2016-13 to have a material impact on our consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-15, *Intangibles – Goodwill and Other – Internal Use Software (Subtopic 350-40)*, to align the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal-use software license). The amendments in the update require an entity in a hosting arrangement that is a service contract to follow the guidance in Subtopic 350-40 to determine which implementation costs to capitalize as an asset related to the service contract and which costs to expense. The new standard is effective for fiscal years and interim periods beginning after December 15, 2019 and can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. Early adoption is permitted. We do not expect the adoption of ASU 2018-15 to have a material impact on our consolidated financial statements.

## ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. However, we believe that our exposure to interest rate risk is not significant as the majority of our investments are short-term in duration and due to the low risk profile of our investments, a 10% change in interest rates would not have a material effect on the total market value of our investment portfolio. We have the ability to hold our marketable securities until maturity, and therefore we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investments.

As of December 31, 2019, we held \$73.4 million in cash, cash equivalents, marketable securities, and restricted cash, all of which was denominated in U.S. dollar assets, and consisting primarily of investments in money market funds, reverse repurchase agreements, commercial paper, and corporate bonds.

We are also exposed to market risk related to changes in foreign currency exchange rates, as a result of entering into transactions denominated in currencies other than U.S. dollars. Due to the uncertain timing of expected payments in foreign currencies, we do not utilize any forward exchange contracts. All foreign transactions settle on the applicable spot exchange basis at the time such payments are made. For the year ended December 31, 2019, a majority of our expenditures were denominated in U.S. dollars. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

**ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA**

**AEGLEA BIOTHERAPEUTICS, INC.**

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## Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Aeglea BioTherapeutics, Inc.

### ***Opinion on the Financial Statements***

We have audited the accompanying consolidated balance sheets of Aeglea BioTherapeutics, Inc. and its subsidiaries (the “Company”) as of December 31, 2019 and 2018, and the related consolidated statements of operations, of comprehensive loss, of changes in stockholders’ equity and of cash flows for each of the three years in the period ended December 31, 2019, including 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 as of December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019 in conformity with accounting principles generally accepted in the United States of America.

### ***Basis for Opinion***

These consolidated financial statements are the responsibility of the Company’s management. Our responsibility is to express an opinion on the Company’s consolidated 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 of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated 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 consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP  
Austin, Texas  
February 24, 2020

We have served as the Company’s auditor since 2014.

**Aeglea BioTherapeutics, Inc.**  
**Consolidated Balance Sheets**

(In thousands, except share and per share amounts)

	December 31,	
	2019	2018
<b>ASSETS</b>		
<b>CURRENT ASSETS</b>		
Cash and cash equivalents	\$ 19,253	\$ 22,461
Marketable securities	52,696	52,052
Prepaid expenses and other current assets	2,556	2,158
Total current assets	74,505	76,671
Restricted cash	1,500	—
Property and equipment, net	2,385	1,018
Operating lease right-of-use assets	4,726	—
Other non-current assets	67	50
<b>TOTAL ASSETS</b>	<b>\$ 83,183</b>	<b>\$ 77,739</b>
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
<b>CURRENT LIABILITIES</b>		
Accounts payable	\$ 3,154	\$ 663
Operating lease liabilities	351	—
Accrued and other current liabilities	14,854	9,576
Total current liabilities	18,359	10,239
Non-current operating lease liabilities	4,712	—
Other non-current liabilities	31	72
<b>TOTAL LIABILITIES</b>	<b>23,102</b>	<b>10,311</b>
Commitments and Contingencies (Note 14)		
<b>STOCKHOLDERS' EQUITY</b>		
Preferred stock, \$0.0001 par value; 10,000,000 shares authorized as of December 31, 2019 and 2018; no shares issued and outstanding as of December 31, 2019 and 2018	—	—
Common stock, \$0.0001 par value; 500,000,000 shares authorized as of December 31, 2019 and 2018, 29,084,437 shares and 24,140,097 shares issued and outstanding as of December 31, 2019 and 2018, respectively	3	2
Additional paid-in capital	255,142	184,314
Accumulated other comprehensive income (loss)	51	(27)
Accumulated deficit	(195,115)	(116,861)
<b>TOTAL STOCKHOLDERS' EQUITY</b>	<b>60,081</b>	<b>67,428</b>
<b>TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY</b>	<b>\$ 83,183</b>	<b>\$ 77,739</b>

The accompanying notes are an integral part of these consolidated financial statements.

**Aeglea BioTherapeutics, Inc.**  
**Consolidated Statements of Operations**

(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2019	2018	2017
<b>Revenues:</b>			
Grant	\$ —	\$ 3,888	\$ 5,205
<b>Operating expenses:</b>			
Research and development	64,600	36,719	22,815
General and administrative	15,734	12,632	10,066
Total operating expenses	80,334	49,351	32,881
Loss from operations	(80,334)	(45,463)	(27,676)
<b>Other income (expense):</b>			
Interest income	2,143	1,172	482
Other expense, net	(63)	(57)	(42)
Total other income	2,080	1,115	440
Net loss	\$ (78,254)	\$ (44,348)	\$ (27,236)
Net loss per share, basic and diluted	\$ (2.45)	\$ (2.13)	\$ (1.80)
Weighted-average common shares outstanding, basic and diluted	31,949,633	20,822,560	15,128,192

The accompanying notes are an integral part of these consolidated financial statements.

**Aeglea BioTherapeutics, Inc.**  
**Consolidated Statements of Comprehensive Loss**

(In thousands)

	Year Ended December 31,		
	2019	2018	2017
Net loss	\$ (78,254)	\$ (44,348)	\$ (27,236)
Other comprehensive income (loss):			
Unrealized gain (loss) on marketable securities	78	75	(98)
Total comprehensive loss	<u>\$ (78,176)</u>	<u>\$ (44,273)</u>	<u>\$ (27,334)</u>

The accompanying notes are an integral part of these consolidated financial statements.



**Aeglea BioTherapeutics, Inc.**  
**Consolidated Statements of Changes in Stockholders' Equity**

(In thousands)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount				
Balances—December 31, 2016	13,431	\$ 1	\$ 108,246	\$ (45,277)	\$ (4)	\$ 62,966
Issuance of common stock in connection with employee stock purchase plan	39	—	131	—	—	131
Issuance of common stock in connection with exercise of stock options	200	—	702	—	—	702
Issuance of common stock in connection with follow-on offering, net of offering costs	3,000	1	11,379	—	—	11,380
Stock-based compensation expense	—	—	2,492	—	—	2,492
Unrealized loss on marketable securities	—	—	—	—	(98)	(98)
Net loss	—	—	—	(27,236)	—	(27,236)
Balances—December 31, 2017	16,670	\$ 2	\$ 122,950	\$ (72,513)	\$ (102)	\$ 50,337
Issuance of common stock in connection with employee stock purchase plan	56	—	207	—	—	207
Issuance of common stock in connection with exercise of stock options	521	—	2,829	—	—	2,829
Issuance of common stock in connection with public and at-the-market offerings, net of offering costs	6,893	—	54,048	—	—	54,048
Stock-based compensation expense	—	—	4,280	—	—	4,280
Unrealized gain on marketable securities	—	—	—	—	75	75
Net loss	—	—	—	(44,348)	—	(44,348)
Balances—December 31, 2018	24,140	\$ 2	\$ 184,314	\$ (116,861)	\$ (27)	\$ 67,428
Issuance of common stock in connection with employee stock purchase plan	45	—	307	—	—	307
Issuance of common stock in connection with exercise of stock options	274	—	1,143	—	—	1,143
Issuance of common stock and pre-funded warrants in connection with public offering, net of offering costs	4,625	1	64,502	—	—	64,503
Stock-based compensation expense	—	—	4,876	—	—	4,876
Unrealized gain on marketable securities	—	—	—	—	78	78
Net loss	—	—	—	(78,254)	—	(78,254)
Balances—December 31, 2019	29,084	\$ 3	\$ 255,142	\$ (195,115)	\$ 51	\$ 60,081

The accompanying notes are an integral part of these consolidated financial statements.

**Aeglea BioTherapeutics, Inc.**  
**Consolidated Statements of Cash Flows**

(In thousands)

	Year Ended December 31,		
	2019	2018	2017
<b>CASH FLOWS FROM OPERATING ACTIVITIES</b>			
Net loss	\$ (78,254)	\$ (44,348)	\$ (27,236)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	418	293	249
Purchase net discount on marketable securities	504	907	9
Net (accretion of discount) amortization of premium on marketable securities	(818)	(593)	75
Stock-based compensation	4,876	4,280	2,492
Research and development services settled with stock	—	107	15
Non-cash operating lease expense	483	—	—
Other, net	(5)	(40)	(21)
Changes in operating assets and liabilities:			
Accounts receivable - grant	—	3,078	(1,863)
Prepaid expenses and other assets	(346)	(261)	(114)
Accounts payable	2,583	239	164
Deferred revenue	—	(20)	(51)
Operating lease liabilities	(258)	—	—
Accrued and other liabilities	5,125	4,165	1,666
Net cash used in operating activities	<u>(65,692)</u>	<u>(32,193)</u>	<u>(24,615)</u>
<b>CASH FLOWS FROM INVESTING ACTIVITIES</b>			
Purchases of property and equipment	(1,492)	(422)	(619)
Purchases of marketable securities	(91,926)	(62,179)	(64,115)
Proceeds from maturities and sales of marketable securities	91,679	47,370	42,205
Net cash used in investing activities	<u>(1,739)</u>	<u>(15,231)</u>	<u>(22,529)</u>
<b>CASH FLOWS FROM FINANCING ACTIVITIES</b>			
Proceeds from issuance of common stock and pre-funded warrants in public and at-the-market offerings, net of offering costs	64,298	54,048	11,380
Proceeds from employee stock plan purchases and stock option exercises	1,450	3,020	833
Principal payments on finance lease obligation	(25)	—	—
Net cash provided by financing activities	<u>65,723</u>	<u>57,068</u>	<u>12,213</u>
<b>NET (DECREASE) INCREASE IN CASH, CASH EQUIVALENTS, AND RESTRICTED CASH</b>	<u>(1,708)</u>	<u>9,644</u>	<u>(34,931)</u>
<b>CASH, CASH EQUIVALENTS, AND RESTRICTED CASH</b>			
Beginning of period	22,461	12,817	47,748
End of period	<u>\$ 20,753</u>	<u>\$ 22,461</u>	<u>\$ 12,817</u>
<b>Supplemental Disclosure of Non-Cash Investing and Financing Information:</b>			
Leased assets obtained in exchange for lease obligations	\$ 5,294	\$ —	\$ —
Unpaid amounts related to purchase of property and equipment	\$ 356	\$ 92	\$ 57

The accompanying notes are an integral part of these consolidated financial statements.

**Aeglea BioTherapeutics, Inc.**  
**Notes to Consolidated Financial Statements**

## **1. The Company and Basis of Presentation**

Aeglea BioTherapeutics, Inc. (“Aeglea” or the “Company”) is a clinical-stage biotechnology company developing next-generation human enzyme therapeutics as disruptive solutions for rare and other high-burden diseases. The Company was formed as a Limited Liability Company (LLC) in Delaware on December 16, 2013 under the name Aeglea BioTherapeutics Holdings, LLC and was converted from a Delaware LLC to a Delaware corporation on March 10, 2015. The Company operates in one segment and has its principal offices in Austin, Texas.

### ***Liquidity***

As of December 31, 2019, the Company had working capital of \$56.1 million, an accumulated deficit of \$195.1 million, and cash, cash equivalents, marketable securities, and restricted cash of \$73.4 million. The Company has not generated any product revenues and has not achieved profitable operations. There is no assurance that profitable operations will ever be achieved, and, if achieved, could be sustained on a continuing basis. In addition, development activities, clinical and nonclinical testing, and commercialization of the Company’s products will require significant additional financing.

The Company is subject to a number of risks similar to other life science companies, including, but not limited to, risks related to the successful discovery, development, and commercialization of product candidates, raising additional capital, development of competing drugs and therapies, protection of proprietary technology and market acceptance of the Company’s products. As a result of these and other factors and the related uncertainties, there can be no assurance of the Company’s future success.

Based upon the Company’s current operating plans, the Company believes that it has sufficient resources to fund operations through the first quarter of 2021 with its existing cash, cash equivalents, and marketable securities. The Company will need to secure additional funding in the future, in order to carry out all of its planned research and development activities. If the Company is unable to obtain additional financing or generate license or product revenue, the lack of liquidity could have a material adverse effect on the Company’s future prospects.

### ***Basis of Presentation***

The consolidated financial statements have been prepared in conformity with generally accepted accounting principles in the United States (“U.S. GAAP”) as defined by the Financial Accounting Standards Board (“FASB”) and include the accounts of the Company and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

## **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 amounts reported in the consolidated financial statements and accompanying notes. Such management estimates include those related to accruals of research and development related costs, stock-based compensation, and certain company income tax related items. Management bases its estimates on historical experience and on various other market-specific and relevant assumptions that management believes to be reasonable under the circumstances. Actual results could differ significantly from those estimates.

### ***Cash and Cash Equivalents***

The Company considers all highly liquid investments with original maturities of three months or less from the date of purchase to be cash equivalents. Cash equivalents consist of money market funds and debt securities and are stated at fair value.

### **Marketable Securities**

All investments have been classified as available-for-sale and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments in debt securities at the time of purchase. The Company may or may not hold securities with stated maturities greater than one year until maturity. All available-for-sale securities are considered available to support current operations and are classified as current assets.

Unrealized gains and losses are excluded from earnings and are reported as a component of accumulated comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in other income (expense). The cost of securities sold is based on the specific-identification method. A realized gain is included in other expense, net for the year ended December 31, 2019. There were no realized gains or losses on marketable securities for the years ended December 31, 2018 and 2017. Interest on marketable securities is included in interest income.

### **Restricted Cash**

Restricted cash consists of a money market account held by a financial institution as collateral for the Company's obligations under its facility lease for the Company's corporate headquarters in Austin, TX.

### **Concentration of Credit Risk**

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, marketable securities, and restricted cash. The Company's investment policy limits investments to high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies, highly rated banks, and corporate issuers, subject to certain concentration limits and restrictions on maturities. The Company's cash, cash equivalents, marketable securities, and restricted cash are held by financial institutions in the United States that management believes are of high credit quality. Amounts on deposit may at times exceed federally insured limits. The Company has not experienced any losses on its deposits of cash, cash equivalents, and restricted cash and its accounts are monitored by management to mitigate risk. The Company is exposed to credit risk in the event of default by the financial institutions holding its cash, cash equivalents, and restricted cash, and bond issuers.

### **Property and Equipment**

Property and equipment are stated at cost, net of accumulated depreciation and amortization. Depreciation and amortization are computed using the straight-line method over the estimated useful lives of the assets. Repairs and maintenance that do not extend the life or improve an asset are expensed as incurred. Upon retirement or sale, the cost of disposed assets and their related accumulated depreciation and amortization are removed from the balance sheet. Any gain or loss is credited or charged to operations.

The useful lives of the property and equipment are as follows:

Laboratory equipment	5 years
Furniture and office equipment	5 years
Computer equipment	3 years
Software	3 years
Leasehold improvements	Shorter of remaining lease term or estimated useful life

### **Impairment of Long-Lived Assets**

Long-lived assets are reviewed for indications of possible impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability is measured by comparison of the carrying amounts to the future undiscounted cash flows attributable to these assets. An impairment loss is recognized to the extent an asset group is not recoverable, and the carrying amount exceeds the projected discounted future cash flows arising from these assets. There were no impairments of long-lived assets for the years ended December 31, 2019, 2018, and 2017.

### ***Accrued Research and Development Costs***

The Company records the costs associated with research nonclinical studies, clinical trials, and manufacturing development as incurred. These costs are a significant component of the Company's research and development expenses, with a substantial portion of the Company's on-going research and development activities conducted by third-party service providers, including contract research and manufacturing organizations.

The Company accrues for expenses resulting from obligations under agreements with contract research organizations ("CROs"), contract manufacturing organizations ("CMOs"), and other outside service providers for which payment flows do not match the periods over which materials or services are provided to the Company. Accruals are recorded based on estimates of services received and efforts expended pursuant to agreements established with CROs, CMOs, and other outside service providers. These estimates are typically based on contracted amounts applied to the proportion of work performed and determined through analysis with internal personnel and external service providers as to the progress or stage of completion of the services. The Company makes significant judgments and estimates in determining the accrual balance in each reporting period. In the event advance payments are made to a CRO, CMO, or outside service provider, the payments will be recorded as a prepaid asset which will be amortized as the contracted services are performed. As actual costs become known, the Company adjusts its accruals. Inputs, such as the services performed, the number of patients enrolled, or the study duration, may vary from the Company's estimates, resulting in adjustments to research and development expense in future periods. Changes in these estimates that result in material changes to the Company's accruals could materially affect the Company's results of operations. Historically, the Company has not experienced any material deviations between accrued and actual research and development expenses.

### ***Leases***

The Company determines if an arrangement is a lease at inception. Right-of-use ("ROU") assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. The classification of the Company's leases as operating or finance leases along with the initial measurement and recognition of the associated ROU assets and lease liabilities is performed at the lease commencement date. The measurement of lease liabilities is based on the present value of future lease payments over the lease term. As the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at the lease commencement date in determining the present value of future lease payments. The ROU asset is based on the measurement of the lease liability and also includes any lease payments made prior to or on lease commencement and excludes lease incentives and initial direct costs incurred, as applicable. The lease terms may include options to extend or terminate the lease when it is reasonably certain the Company will exercise any such options. Rent expense for the Company's operating leases is recognized on a straight-line basis over the lease term. Amortization expense for the ROU asset associated with its finance leases is recognized on a straight-line basis over the term of the lease and interest expense associated with its finance leases is recognized on the balance of the lease liability using the effective interest method based on the estimated incremental borrowing rate.

The Company has lease agreements with lease and non-lease components. As allowed under Topic 842, the Company has elected to not separate lease and non-lease components for any leases involving real estate and office equipment classes of assets and, as a result, accounts for the lease and non-lease components as a single lease component. The Company has also elected to not apply the recognition requirement of Topic 842 to leases with a term of 12 months or less for all classes of assets.

### ***Fair Value of Financial Instruments***

The Company uses fair value measurements to record fair value adjustments to certain financial and non-financial assets and liabilities and to determine fair value disclosures. The accounting standards define fair value, establish a framework for measuring fair value, and require disclosures about fair value measurements. Fair value is defined as the price that would be received from selling an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. When determining the fair value measurements for assets and liabilities required to be recorded at fair value, the principal or most advantageous market in which the Company would transact are considered along with assumptions that market participants would use when pricing the asset or liability, such as inherent risk, transfer restrictions, and risk of nonperformance.

The accounting standard for fair value establishes a fair value hierarchy based on three levels of inputs, the first two of which are considered observable and the last unobservable, that requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. A financial instrument's categorization within the fair value hierarchy is based upon the lowest level of input that is significant to the fair value measurement.

The three levels of inputs that may be used to measure fair value are as follows:

- Level 1: Observable inputs, such as quoted prices in active markets for identical assets or liabilities.
- Level 2: Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.
- Level 3: Valuations based on unobservable inputs to the valuation methodology and including data about assumptions that market participants would use in pricing the asset or liability based on the best information available under the circumstances.

Financial instruments carried at fair value include cash, cash equivalents, marketable securities, and restricted cash. The carrying amount of accounts receivable, accounts payable and accrued liabilities approximate fair value due to their relatively short maturities.

### ***Revenue Recognition***

The Company's sole source of revenue was grant revenue related to a \$19.8 million research grant received from the Cancer Prevention and Research Institute of Texas ("CPRIT"), covering a four-year period from June 1, 2014 through May 31, 2018. Grant revenue was recognized when qualifying costs were incurred and there was reasonable assurance that the conditions of the award had been met for collection. Proceeds received prior to the costs being incurred or the conditions of the award being met were recognized as deferred revenue until the services were performed and the conditions of the award were met (see Note 9).

### ***Research and Development Costs***

Research and development costs are expensed as incurred. Research and development costs include, but are not limited to, salaries, benefits, travel, stock-based compensation, consulting costs, contract research service costs, laboratory supplies and facilities, contract manufacturing costs, and costs paid to other third parties that conduct research and development activities on the Company's behalf. Amounts incurred in connection with license agreements are also included in research and development expense.

Advance payments for goods or services to be rendered in the future for use in research and development activities are recorded as a prepaid asset and expensed as the related goods are delivered or the services are performed.

### ***Stock-Based Compensation***

The Company recognizes the cost of stock-based awards granted to employees and non-employees based on the estimated grant-date fair values of the awards. The value of the award is recognized as compensation expense on a straight-line basis over the requisite service period. Forfeitures are recognized when they occur, which may result in the reversal of compensation costs in subsequent periods as the forfeitures arise. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable.

### ***Income Taxes***

The Company and its seven wholly-owned U.S. subsidiary corporations use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. Additionally, any changes in income tax laws are immediately recognized in the year of enactment.

A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to a lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. The Company's policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense.

### Comprehensive Loss

Comprehensive loss is the change in stockholders' equity from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company's other comprehensive income (loss) is currently comprised of changes in unrealized gains and losses on available-for-sale securities.

### Recent Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), which establishes a comprehensive new lease accounting model. The new standard: (a) clarifies the definition of a lease; (b) requires a dual approach to lease classification similar to current lease classifications; and (c) causes lessees to recognize leases on the balance sheet as a lease liability with a corresponding right-of-use (ROU) asset. On January 1, 2019, the Company adopted Topic 842 using the modified retrospective approach as of the adoption date in accordance with ASU No. 2018-11, Leases (Topic 842): Targeted Improvements. Results for the year ended December 31, 2019 are presented under Topic 842. No prior period amounts were adjusted and continue to be reported in accordance with previous lease guidance, ASC Topic 840, Leases. The Company elected all of the available practical expedients permitted under the transition guidance within the new standard, which among other things, allowed the Company to carry forward the historical lease classification of those leases in place as of January 1, 2019.

The following table summarizes the impact of the adoption of Topic 842 on the accompanying balance sheet as of January 1, 2019 (in thousands):

	December 31, 2018	Effect of the Adoption of Topic 842	January 1, 2019
Other non-current assets <sup>(1)</sup>	\$ 50	\$ 691	\$ 741
<b>Lease Liabilities:</b>			
Current operating lease liabilities	\$ —	\$ 339	\$ 339
Non-current operating lease liabilities	\$ —	\$ 465	\$ 465
Accrued and other current liabilities <sup>(2)</sup>	\$ 9,576	\$ (41)	\$ 9,535
Other non-current liabilities <sup>(3)</sup>	\$ 72	\$ (72)	\$ —

(1) Operating lease right-of-use assets are classified within other non-current assets.

(2) Current deferred rent was classified within accrued and other current liabilities as of December 31, 2018.

(3) Non-current deferred rent was classified within other non-current liabilities as of December 31, 2018.

The adjustments due to the adoption of Topic 842 related to the recognition of operating lease right-of-use assets and lease liabilities for the existing operating leases. A cumulative-effect adjustment to the beginning accumulated deficit balance was not required.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments-Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*, which changes the impairment model for most financial assets and certain other instruments. For available-for-sale debt securities with unrealized credit losses, the credit losses will be recognized as allowances rather than as reductions in the amortized cost of the securities. The guidance is effective for interim and annual periods beginning after December 15, 2019. The guidance and its amendments will be applied using a modified retrospective approach with the cumulative effect recognized as an adjustment to retained earnings. The Company does not expect the adoption of ASU 2016-13 to have a material impact on its consolidated financial statements.

In August 2018, the FASB issued ASU No. 2018-15, *Intangibles – Goodwill and Other – Internal Use Software (Subtopic 350-40)*, to align the requirements for capitalizing implementation costs incurred in a hosting arrangement that is a service contract with the requirements for capitalizing implementation costs incurred to develop or obtain internal-use software (and hosting arrangements that include an internal-use software license). The amendments in the update require an entity in a hosting arrangement that is a service contract to follow the guidance in Subtopic 350-40 to determine which implementation costs to capitalize as an asset related to the service contract and which costs to expense. The new standard is effective for fiscal years and interim periods beginning after December 15, 2019 and can be applied either retrospectively or prospectively to all implementation costs incurred after the date of adoption. Early adoption is permitted. The Company does not expect the adoption of ASU 2018-15 to have a material impact on its consolidated financial statements.

### 3. Fair Value Measurements

The Company measures and reports certain financial instruments as assets and liabilities at fair value on a recurring basis. The following tables sets forth the fair value of the Company's financial assets and liabilities at fair value on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	December 31, 2019			
	Level 1	Level 2	Level 3	Total
<b>Financial Assets</b>				
Money market funds	\$ 7,023	\$ —	\$ —	\$ 7,023
Reverse repurchase agreements	—	6,250	—	6,250
Commercial paper	—	15,193	—	15,193
Corporate bonds	—	39,750	—	39,750
<b>Total financial assets</b>	<b>\$ 7,023</b>	<b>\$ 61,193</b>	<b>\$ —</b>	<b>\$ 68,216</b>

	December 31, 2018			
	Level 1	Level 2	Level 3	Total
<b>Financial Assets</b>				
Money market funds	\$ 7,180	\$ —	\$ —	\$ 7,180
Reverse repurchase agreements	—	6,250	—	6,250
Commercial paper	—	53,916	—	53,916
U.S. government securities	—	4,112	—	4,112
<b>Total financial assets</b>	<b>\$ 7,180</b>	<b>\$ 64,278</b>	<b>\$ —</b>	<b>\$ 71,458</b>

The Company measures the fair value of money market funds and U.S. treasury securities on quoted prices in active markets for identical asset or liabilities. The Level 2 assets include reverse repurchase agreements, U.S. government securities, commercial paper, and corporate bonds and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data.

The Company evaluates transfers between levels at the end of each reporting period. There were no transfers between Level 1 and Level 2 during the periods presented.

### 4. Cash Equivalents and Marketable Securities

The following tables summarize the estimated fair value of the Company's cash equivalents and marketable securities and the gross unrealized gains and losses (in thousands):

	December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
<b>Cash equivalents:</b>				
Money market funds	\$ 7,023	\$ —	\$ —	\$ 7,023
Reverse repurchase agreements	6,250	—	—	6,250
Commercial paper	2,247	—	—	2,247
<b>Total cash equivalents</b>	<b>15,520</b>	<b>—</b>	<b>—</b>	<b>15,520</b>
<b>Marketable securities:</b>				
Commercial paper	12,931	15	—	12,946
Corporate bonds	39,714	45	(9)	39,750
<b>Total marketable securities</b>	<b>\$ 52,645</b>	<b>\$ 60</b>	<b>\$ (9)</b>	<b>\$ 52,696</b>



	December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
<b>Cash equivalents:</b>				
Money market funds	\$ 7,180	\$ —	\$ —	\$ 7,180
Reverse repurchase agreements	6,250	—	—	6,250
Commercial paper	5,977	—	(1)	5,976
<b>Total cash equivalents</b>	<b>19,407</b>	<b>—</b>	<b>(1)</b>	<b>19,406</b>
<b>Marketable securities:</b>				
Commercial paper	47,964	—	(24)	47,940
U.S. government securities	4,114	—	(2)	4,112
<b>Total marketable securities</b>	<b>\$ 52,078</b>	<b>\$ —</b>	<b>\$ (26)</b>	<b>\$ 52,052</b>

The reverse repurchase agreements are settled in cash nightly, and as such are classified as cash equivalents.

As of December 31, 2019 and 2018, all debt securities with an unrealized loss position have been in a loss position for less than one year. The aggregate fair value of debt securities in an unrealized loss position as of December 31, 2019 and 2018 were \$13.0 million and \$45.6 million, respectively, with no individual securities in a significant unrealized loss position. The Company evaluated its securities for other-than-temporary impairment and considered the decline in market value for the securities to be primarily attributable to current economic and market conditions and would not be required to sell the securities before recovery of the amortized cost basis. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of December 31, 2019 and 2018.

The following table summarizes the contractual maturities of the Company's marketable securities at estimated fair value (in thousands):

	December 31,	
	2019	2018
Due in one year or less	\$ 49,687	\$ 52,052
Due in 1 - 2 years	3,009	—
<b>Total marketable securities</b>	<b>\$ 52,696</b>	<b>\$ 52,052</b>

The Company may sell investments at any time for use in current operations even if they have not yet reached maturity. As a result, the Company classifies marketable securities, including securities with maturities beyond twelve months as current assets.

## 5. Property and Equipment, Net

Property and equipment, net consist of the following (in thousands):

	December 31,	
	2019	2018
Laboratory equipment	\$ 1,085	\$ 981
Furniture and office equipment	396	227
Computer equipment	50	89
Software	96	99
Leasehold improvements	1,813	374
Property and equipment, gross	3,440	1,770
Less: Accumulated depreciation and amortization	(1,055)	(752)
<b>Property and equipment, net</b>	<b>\$ 2,385</b>	<b>\$ 1,018</b>

Depreciation and amortization expense for the years ended December 31, 2019, 2018, and 2017 was \$0.4 million, \$0.3 million, and \$0.2 million, respectively. All of the Company's long-lived assets are located in the United States.

## 6. Accrued and Other Current Liabilities

Accrued and other current liabilities consist of the following (in thousands):

	December 31,	
	2019	2018
Accrued compensation	\$ 3,273	\$ 2,643
Accrued contracted research and development costs	10,485	5,993
Accrued professional and consulting fees	627	807
Accrued and other current liabilities	469	133
Total accrued and other current liabilities	<u>\$ 14,854</u>	<u>\$ 9,576</u>

## 7. Leases

The Company leases certain office space, laboratory facilities, and equipment. These leases require monthly lease payments that may be subject to annual increases throughout the lease term. Certain of these leases also include renewal options at the election of the Company to renew or extend the lease for an additional three to five years. These optional periods have not been considered in the determination of the right-of-use-assets or lease liabilities associated with these leases as the Company did not consider it reasonably certain it would exercise the options. The Company performed evaluations of its contracts and determined it has both operating and finance leases.

In April 2019, the Company entered into a lease agreement (the "Las Cimas Lease") for its corporate headquarters and laboratory space located in Austin, TX. The Las Cimas Lease includes approximately 30,000 square feet and commenced on April 30, 2019, with an expiration on April 30, 2028. The Company posted a customary letter of credit in the amount of \$1.5 million as security, which is subject to automatic reductions per the terms of the Las Cimas Lease. A tenant allowance of up to \$1.0 million is provided by the lessor.

The following table summarizes the Company's recognition of its operating and finance leases (in thousands):

	Classification	December 31, 2019
<b>Assets</b>		
Operating	Operating lease right-of-use assets	\$ 4,726
Finance	Other non-current assets	56
Total leased assets		<u>4,782</u>
<b>Leases</b>		
Current		
Operating	Operating lease liabilities	351
Finance	Accrued and other current liabilities	28
Non-current		
Operating	Non-current operating lease liabilities	4,712
Finance	Other non-current liabilities	31
Total lease liabilities		<u>\$ 5,122</u>

The following table summarizes the weighted-average remaining lease term and discount rates for the Company's operating and finance leases:

	December 31, 2019
<b>Lease term (years)</b>	
Operating leases	7.7
Finance leases	2.0
<b>Discount rate</b>	
Operating leases	10.6%
Finance leases	9.5%

The Company incurred rent expense for its operating leases of \$1.3 million, \$0.4 million, and \$0.4 million during the years ended December 31, 2019, 2018, and 2017, respectively, included within operating expenses in the results of operations. Cash paid for amounts included in the measurement of operating lease liabilities during the year ended December 31, 2019 was \$0.7 million and was included within net cash used in operating activities in the cash flows.

The maturities of the Company's operating and finance lease liabilities as of December 31, 2019 were as follows (in thousands):

	Operating Leases	Finance Leases
2020	\$ 1,167	\$ 32
2021	1,061	32
2022	1,007	—
2023	1,037	—
2024	1,069	—
Thereafter	3,796	—
Total lease payments	9,137	64
Less:		
Imputed interest	(3,070)	(5)
Tenant allowance	(1,004)	—
Total	<u>\$ 5,063</u>	<u>\$ 59</u>

As of December 31, 2018, future annual minimum lease payments, as defined under the previous lease accounting guidance of ASC Topic 840, due under non-cancelable operating leases at December 31 of each year are as follows (in thousands):

2019	\$ 397
2020	409
2021	83
Thereafter	—
Total minimum lease payments	<u>\$ 889</u>

## 8. Stockholders' Equity

The Company is authorized to issue 510,000,000 shares of capital stock of which 500,000,000 shares are designated as common stock and 10,000,000 shares are designated as preferred stock, all with a par value of \$0.0001 per share. Each holder of common stock is entitled to one vote for each share of common stock held. The Company's common stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions. Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of common stock are entitled to receive dividends out of funds legally available if the board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that the board of directors may determine. As of December 31, 2019 and 2018, no common stock dividends had been declared by the board of directors and there were no shares of preferred stock outstanding.

### *Follow-on Public Offerings*

In June 2017, the Company issued and sold 3,000,000 shares of common stock in an underwritten public offering pursuant to a shelf registration statement on Form S-3 at a public offering price of \$4.10 per share. The net proceeds to the Company from this public offering was \$11.4 million, after deducting underwriting discounts and commissions of \$0.6 million and offering costs of \$0.3 million.

In April 2018, the Company issued and sold 5,046,510 shares of common stock in an underwritten public offering pursuant to a shelf registration statement on Form S-3 at a public offering price of \$8.00 per share, including 546,510 shares of common stock issued upon the partial exercise by the underwriters of their option to purchase additional shares. The net proceeds to the Company from this public offering was \$37.7 million, after deducting underwriting discounts and commissions of \$2.4 million and offering costs of \$0.3 million.

In February 2019, the Company issued and sold 4,625,000 shares of common stock at a public offering price of \$8.00 per share and pre-funded warrants to purchase up to 4,000,000 shares of common stock at a public offering price of \$7.9999 per warrant in an underwritten public offering pursuant to a shelf registration statement on Form S-3. This includes the full exercise by the underwriters of their option to purchase up to 1,125,000 additional shares of common stock. The net proceeds to the Company from this offering were \$64.5 million, after deducting underwriting discounts and commissions of \$4.1 million and offering costs of \$0.4 million.

The public offering price for the pre-funded warrants was equal to the public offering price of the common stock, less the \$0.0001 per share exercise price of each warrant. These warrants were recorded as a component of stockholders' equity within additional paid-in capital and have no expiration date. Per the terms of the warrant agreement, the outstanding warrants to purchase shares of common stock may not be exercised if the holder's ownership of the Company's common stock would exceed 4.99% ("Maximum Ownership Percentage"). By written notice to the Company, the holders may increase or decrease the Maximum Ownership Percentage. The revised Maximum Ownership Percentage would be effective 61 days after the notice is received by the Company. As of December 31, 2019, none of the pre-funded warrants have been exercised.

### ***At-The-Market Offering***

In May 2017, the Company entered into a sales agreement with JonesTrading Institutional Services LLC, as sales agent and underwriter, pursuant to which the Company may issue and sell shares of its common stock for an aggregate offering price of \$20.0 million under an at-the-market ("ATM") offering program. In October 2018, the Company sold 1,845,820 shares of common stock in a single transaction pursuant to the ATM at an offering price of \$9.21 per share for gross proceeds of \$17.0 million, resulting in net proceeds of \$16.4 million after deducting underwriting fees and offering expenses.

The Company subsequently terminated the ATM sales agreement with JonesTrading in December 2018 and entered into a sales agreement with Jeffries LLC, as sales agent and underwriter, to issue and sell shares of the Company's common stock for an aggregate offering price of \$60.0 million under an ATM offering program. As of December 31, 2019, \$60.0 million of the Company's common stock remained available for sale.

## **9. Grant Revenues**

In June 2015, the Company entered into a Cancer Research Grant Contract ("Grant Contract") with CPRIT, under which CPRIT awarded a grant not to exceed \$19.8 million for use in developing cancer treatments by exploiting the metabolism of cancer cells. The Grant Contract covered a four-year period from June 1, 2014 through May 31, 2018.

Upon commercialization of the product, the terms of the Grant Contract require the Company to pay tiered royalties in the low to mid-single digit percentages. Such royalties reduce to less than one percent after a mid-single-digit multiple of the grant funds have been paid to CPRIT as royalties.

The contract ended in May 2018 with the full \$19.8 million grant recognized as revenue over the life of the award. For the year ended December 31, 2019, the Company recognized no grant revenue. For the years ended December 31, 2018 and 2017, the Company recognized \$3.9 million, and \$5.2 million, respectively, in grant revenues for qualified expenditures under the grant. As of December 31, 2018, all grant proceeds had been collected.

## **10. Stock-Based Compensation**

### ***2015 Equity Incentive Plan***

In March 2015, the Company adopted the 2015 Equity Incentive Plan ("2015 Plan"), administered by the board of directors, and provides for the Company to sell or issue common stock or restricted common stock, or to grant incentive stock options or nonqualified stock options for the purchase of common stock, to employees, members of the board of directors and consultants of the Company. Under the terms of the 2015 Plan, the exercise prices, vesting and other restrictions may be determined at the discretion of the board of directors, or their committee if so delegated, except that the exercise price per share of stock options may not be less than 100% of the fair market value of the share of common stock on the date of grant, the term of stock options may not be greater than ten years for all grants, and for grantees holding more than 10% of the total combined voting power of all classes of stock, the term may not be greater than five years.

The Company granted options under the 2015 Plan until April 2016 when it was terminated as to future awards, although it continues to govern the terms of options that remain outstanding under the 2015 Plan.

As of December 31, 2019, a total of 250,286 shares of common stock are subject to options outstanding under the 2015 Plan and will become available under the 2016 Equity Incentive Plan (“2016 Plan”) to the extent the options are forfeited or lapse unexercised.

### ***2016 Equity Incentive Plan***

The 2016 Plan became effective in April 2016 and serves as the successor to the 2015 Plan. Under the 2016 Plan, the Company may grant stock options, stock appreciation rights, restricted stock awards, restricted stock units, performance awards, and stock bonuses. The 2016 Plan provides for an initial reserve of 1,100,000 shares of common stock, plus 509,869 shares of common stock remaining under the 2015 Plan, and any share awards that subsequently are forfeited or lapse unexercised under the 2015 Plan. The shares reserved exclude shares of common stock reserved for issuance under the 2015 Plan.

In October 2018, the 2016 plan was amended to increase the number of shares of common stock reserved for issuance thereunder by 1,759,602 shares, extend the term of the 2016 Plan through August 7, 2028, and provide for an automatic increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the plan equal to (a) 4.0% of the number of issued and outstanding shares of common stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the board each year. The superseded 2016 Plan provision to provide an annual increase in the number of shares available for issuance required the Company’s board of directors to approve the increase, up to 4%, prior to January 1 of each relevant year. As a result of the operation of each of these provisions, on January 1, 2019, 2018, and 2017, an additional 965,603, 666,807, and 537,233 shares, respectively, became available for issuance under the 2016 Plan.

As of December 31, 2019, the total number of shares reserved for issuance under the 2016 Plan was 5,721,946, of which 3,538,992 shares were subject to outstanding option awards.

### ***2018 Equity Inducement Plan***

In February 2018, the board of directors approved and adopted the 2018 Equity Inducement Plan (“2018 Plan”), which became effective on the same date. The board of directors approved an initial reserve of 1,100,000 shares of common stock to be used exclusively for individuals who were not previously employees or directors, or following a bona fide period of non-employment, as an inducement material to the individual entering into employment with the Company. Nonqualified stock options or restricted stock units may be granted under the 2018 Plan at the discretion of the Compensation Committee or the board of directors. The Company did not seek stockholder approval of the 2018 Plan pursuant to Nasdaq Rule 5635(c)(4).

As of December 31, 2019, the total number of shares reserved for issuance under the 2018 Plan was 1,100,000, of which 99,910 shares were subject to outstanding option awards.

Under the 2016 Plan and 2018 Plan, the Company may grant stock-based awards with service conditions (“service-based” awards), performance conditions (“performance-based” awards), and market conditions (“market-based” awards). Service-based awards granted under the 2018 Plan, 2016 Plan, and 2015 Plan generally vest over four years and expire after ten years, although awards have been granted with vesting terms less than four years.

### ***2016 Employee Stock Purchase Plan***

The 2016 Employee Stock Purchase Plan (“2016 ESPP”) became effective in April 2016. A total of 165,000 shares of common stock were reserved for issuance under the 2016 ESPP. Eligible employees may purchase shares of common stock under the 2016 ESPP at 85% of the lower of the fair market value of the Company’s common stock as of the first or the last day of each offering period. Employees are limited to contributing 15% of the employee’s eligible compensation and may not purchase more than \$25,000 of stock during any calendar year or more than 2,000 shares during any one purchase period or a lesser amount determined by the board of directors. The 2016 ESPP will terminate ten years from the first purchase date under the plan, unless terminated earlier by the board of directors.

In June 2018, the 2016 ESPP was amended to provide for an automatic annual increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the year equal to (a) 1.0% of the number of issued and outstanding shares of common stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the board of directors each year. As a result of the operation of this provision, on January 1, 2019, an additional 241,400 shares became available for issuance under the 2016 ESPP. As of December 31, 2019, the reserve remaining and available for future issuance under the 2016 ESPP was 247,347 shares.

The following table summarizes employee and non-employee stock option activity for the year ended December 31, 2019:

	Shares Issuable Under Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
<b>Outstanding as of December 31, 2018</b>	3,142,687	\$ 6.67	8.52	\$ 4,798
Granted	1,516,900	8.09		
Exercised	(274,436)	4.16		
Forfeited	(495,963)	6.94		
<b>Outstanding as of December 31, 2019</b>	<u>3,889,188</u>	\$ 7.37	8.10	\$ 3,642
<b>Options vested and expected to vest as of December 31, 2019</b>	<u>3,762,950</u>	\$ 7.31	8.09	\$ 3,637
<b>Options exercisable as of December 31, 2019</b>	<u>1,767,376</u>	\$ 6.67	7.25	\$ 2,774

The aggregate intrinsic value of options outstanding, exercisable, vested and expected to vest were calculated as the difference between the exercise price of the options and the fair value of the Company's common stock as of the reporting date.

For the years ended December 31, 2019, 2018, and 2017, the weighted-average grant date fair value of options granted was \$8.09, \$8.03, and \$5.22, respectively. The total intrinsic value of options exercised during the years ended December 31, 2019, 2018, and 2017 was \$1.0 million, \$1.9 million and \$0.3 million, respectively.

There were no stock options issued to non-employees during the years ended December 31, 2019, 2018, and 2017. For the year ended December 31, 2018, 6,626 non-employee stock options vested in the period. For the years ended December 31, 2019 and 2017, no non-employee stock options vested in the period.

### Stock-Based Compensation Expense

Total stock-based compensation expense recognized from the Company's equity incentive plans, 2018 Plan, and the 2016 ESPP for the years ended December 31, 2019, 2018, and 2017 was as follows (in thousands):

	Year Ended December 31,					
	2019		2018		2017	
	Employees	Non-Employees	Employees	Non-Employees	Employees	Non-Employees
Research and development	\$ 1,828	\$ —	\$ 1,440	\$ 234	\$ 961	\$ —
General and administrative	3,048	—	2,606	—	1,531	—
<b>Total stock-based compensation expense</b>	<u>\$ 4,876</u>	<u>\$ —</u>	<u>\$ 4,046</u>	<u>\$ 234</u>	<u>\$ 2,492</u>	<u>\$ —</u>

No related tax benefits were recognized for the years ended December 31, 2019, 2018, and 2017 (see Note 12).

The employee and non-employee awards contain both performance and service-based vesting conditions. No expense was recognized for the unvested employee and non-employee awards with only a performance condition for the years ended December 31, 2019, 2018, and 2017. The performance-based vesting conditions represent specific performance targets. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable.

In November 2018, one of the board of directors resigned. Upon his resignation, the Company's board of directors approved the immediate vesting of all unvested stock options and restricted stock and an extension in the exercise period for all outstanding equity awards from 90 days to 180 days. The result was a modification of 86,252 outstanding stock options and 43,290 restricted stock awards. The incremental fair value of \$0.3 million, in connection with the modification of the awards, was recognized as stock compensation expense upon resignation with no future service or performance conditions required.

As of December 31, 2019, the Company had an aggregate of \$10.8 million of unrecognized stock-based compensation expense for options outstanding, which is expected to be recognized over a weighted average period of 2.6 years.

In determining the fair value of the stock-based awards, the Company uses the Black-Scholes option-pricing model and assumptions discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

### ***Expected Term***

The Company's expected term represents the period that the Company's stock-based awards are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term). The Company utilizes this method due to lack of historical exercise data and the plain-vanilla nature of the Company's stock-based awards.

### ***Expected Volatility***

Since the Company was privately held through April 2016, it alone does not have the relevant company-specific historical data to support its expected volatility. As such, the Company has used an average of expected volatilities based on the volatilities of a representative group of publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. Subsequent to the Company's initial public offering, it began to consider the Company's own historic volatility. However, due to its limited history as a public company, the Company still uses peer company data to assist in this analysis. For purposes of identifying comparable companies, the Company selected companies with comparable characteristics to it, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The historical volatility data was computed using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. The Company intends to consistently apply this process using the same or similar comparable entities until a sufficient amount of historical information regarding the volatility of the Company's own share price becomes available.

### ***Risk-Free Interest Rate***

The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

### ***Expected Dividend***

The Company has never paid dividends on its common stock and has no plans to pay dividends on its common stock. Therefore, the Company used an expected dividend yield of zero.

The fair value of the stock options granted under the 2018 Plan, 2016 Plan, and 2015 Plan and the shares available for purchase under the 2016 ESPP were determined using the Black-Scholes option-pricing model. The following table summarizes the weighted-average assumptions used in calculating the fair value of the awards:

	Year Ended December 31,		
	2019	2018	2017
<b>2018 Plan, 2016 Plan, and 2015 Plan</b>			
Expected term (in years)	6.01	5.20	5.88
Expected volatility	80%	74%	86%
Risk-free interest	2.32%	2.42%	2.00%
Dividend yield	0%	0%	0%
<b>2016 ESPP</b>			
Expected term (in years)	0.50	0.50	0.50
Expected volatility	70%	66%	78%
Risk-free interest	2.11%	2.20%	1.06%
Dividend yield	0%	0%	0%

## 11. Defined Contribution Plan

In September 2016, the Company began to sponsor a 401(k) retirement plan in which substantially all of its full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. During the years ended December 31, 2019, 2018, 2017, the Company provided \$0.3 million, \$0.2 million, and \$0.1 million, respectively, in contributions to the plan.

## 12. Income Taxes

For the years ended December 31, 2019, 2018, and 2017, the Company recognized no provision or benefit from income taxes. The difference between the Company's provision for income taxes and the amounts computed by applying the statutory federal income tax rate to income before income taxes is as follows (in thousands):

	Year Ended December 31,		
	2019	2018	2017
Tax provision derived by applying the federal statutory rate to income before income taxes	\$ (16,433)	\$ (9,313)	\$ (9,260)
Permanent differences and other	(98)	264	296
Federal tax credits	(3,599)	(1,211)	(1,294)
State tax credits	(229)	464	(284)
Change in tax rate	—	—	7,869
Change in the valuation allowance	20,359	9,796	2,673
Income tax expense /(benefit)	\$ —	\$ —	\$ —



The components of the deferred tax assets and liabilities consist of the following (in thousands):

	December 31,	
	2019	2018
<b>Deferred tax assets</b>		
Net operating loss carryforward	\$ 36,093	\$ 20,276
Intangible assets	45	38
Accrued expense	605	508
Stock-based compensation	1,237	682
Federal tax credits	10,859	7,260
State tax credits	588	359
Other	126	73
<b>Total deferred tax assets</b>	<b>49,553</b>	<b>29,196</b>
<b>Deferred tax liabilities</b>		
Depreciable assets	\$ (72)	\$ (74)
Total deferred tax liabilities	(72)	(74)
Less: Valuation allowance	(49,481)	(29,122)
<b>Deferred tax assets, net</b>	<b>\$ —</b>	<b>\$ —</b>

On December 22, 2017, the 2017 Tax Act was signed into law making significant changes to the Internal Revenue Code. The legislation significantly changed U.S. tax law by, among other things, lowering corporate income tax rates from a maximum of 35% to a flat 21% rate and reducing the orphan drug credit from 50% to 25% of qualifying expenditures, effective for tax years beginning after December 31, 2017. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to reverse. As a result of the reduction in the U.S. corporate income tax rate under the 2017 Tax Act, the Company revalued its deferred tax assets and liabilities as of December 31, 2017 resulting in a \$7.9 million decrease in net deferred assets, with a corresponding reduction in the valuation allowance. The accounting for the income tax effects of the 2017 Tax Act and related adjustments were completed and included in the financial statements as of and for the year ended December 31, 2017. There were no other income tax effects from the 2017 Tax Act for the years ended December 31, 2019 and 2018.

The Company has established a full federal and state valuation allowance equal to the net deferred tax assets due to uncertainties regarding the realization of the deferred tax asset based on the Company's lack of earnings history. The valuation allowance increased by \$20.4 million, \$9.8 million, and \$2.7 million during the years ended December 31, 2019, 2018, and 2017, respectively, primarily due to continuing loss from operations.

As of December 31, 2019 and 2018, the Company had U.S. net operating loss carryforwards ("NOL") of \$171.9 million and \$96.6 million, respectively. As of December 31, 2019 and 2018, the Company had U.S. tax credit carryforwards of \$10.9 million and \$7.3 million, respectively, and state tax credit carryforwards of \$0.6 million and \$0.4 million, respectively. The net operating loss and tax credit carryforwards of \$58.4 million and \$10.9 million, respectively, will begin to expire in 2033, if not utilized. The net operating loss and credit carryforwards are subject to Internal Revenue Service adjustments until the statute closes on the year the net operating loss or tax credits are utilized.

The Company has not completed a study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since the Company's formation due to the complexity and cost associated with such a study, and the fact that there may be additional such ownership changes in the future. If the Company has experienced an ownership change at any time since its formation, utilization of the NOL or R&D credit carryforwards would be subject to an annual limitation under Section 382 or 383 of the Internal Revenue Code, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term, tax-exempt rate, and then could be subject to additional adjustments, as required. Additionally, the separate return limitation year ("SRLY") rules may apply to losses of the Company's seven wholly-owned U.S. subsidiary corporations. The SRLY rules limit the consolidated group's use of a subsidiary corporation's net operating losses to the amount of income generated by the subsidiary corporation after it becomes a member of the group. Any limitation may result in expiration of a portion of the NOL or R&D credit carryforwards before utilization. Further, until a study is completed and any limitation known, no amounts are being considered as an uncertain tax position or disclosed as an unrecognized tax benefit. Additionally, the Company does not expect any unrecognized tax benefits to change significantly over the next twelve months. Due to the existence of the valuation allowance, future changes in the Company's unrecognized tax benefits will not impact its effective tax rate. Any carryforwards that will expire prior to utilization as a result of such limitations will be removed from deferred tax assets with a corresponding reduction of the valuation allowance.

The Company files income tax returns in the U.S. and state jurisdictions. The Company is subject to examination by taxing authorities in its significant jurisdictions for the 2015 and subsequent years. However, due to NOL and tax attribute carryovers, the taxing authorities have the ability to adjust the NOLs and other tax attributes related to closed years. As of December 31, 2019 and 2018, there were no amounts recorded for uncertain tax positions.

### 13. Net Loss Per Share

Basic and diluted net loss per share is computed by dividing net loss by the weighted-average number of common stock and pre-funded warrants outstanding during the period. The pre-funded warrants are included in the computation of basic net loss per share as the exercise price is negligible and they are fully vested and exercisable. For periods in which the Company generated a net loss, the Company does not include the potential impact of dilutive securities in diluted net loss per share, as the impact of these items is anti-dilutive.

The following weighted-average equity instruments were excluded from the calculation of diluted net loss per share because their effect would have been anti-dilutive for the periods presented:

	Year Ended December 31,		
	2019	2018	2017
Options to purchase common stock	3,874,817	3,014,984	2,043,420

### 14. Research and License Agreements

#### *License Agreements*

In December 2013, two of the Company's wholly owned subsidiaries, AECCase, Inc. ("AECCase") and AEMase, Inc. ("AEMase"), entered into license agreements with the University of Texas at Austin (the "University") under which the University granted to AECCase and AEMase exclusive, worldwide, sublicenseable licenses. The University granted the AECCase license under a patent application relating to the right to use technology related to the Company's AEB3103 product candidate. The University granted the AEMase license under a patent relating to the right to use technology related to the Company's AEB2109 product candidate.

In January 2017, the Company entered into an Amended and Restated Patent License Agreement (the "Restated License") with the University which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to the Company. Pursuant to the terms of the Restated License, the Company may be required to pay the University up to \$6.4 million in milestone payments based on the achievement of certain development milestones, including clinical trials and regulatory approvals, the majority of which are due upon the achievement of later development milestones, including a \$5.0 million payment due on regulatory approval of a product and a \$0.5 million payment payable on final regulatory approval of a product for a second indication. In addition, the Company is required to pay the University a low single-digit royalty on worldwide-net sales of products covered under Restated License, together with a revenue share on non-royalty consideration received from sublicensees. The rate of the revenue share ranges from 6.5% to 25% depending on the date the sublicense agreement is signed.

For the years ended December 31, 2019, 2018 and 2017, the Company paid \$50,000, \$50,000 and \$30,000, respectively, in annual license fees.

## 15. Selected Quarterly Financial Data (Unaudited)

Selected quarterly results from operations for the years ended December 31, 2019 and 2018 are as follows (in thousands, except per share amounts):

	2019 Quarter Ended			
	March 31,	June 30,	September 30,	December 31,
Loss from operations	\$ (17,657)	\$ (18,622)	\$ (22,146)	\$ (21,909)
Net loss	(17,167)	(18,019)	(21,573)	(21,495)
Basic and diluted net loss per common share	\$ (0.59)	\$ (0.55)	\$ (0.66)	\$ (0.65)

	2018 Quarter Ended			
	March 31,	June 30,	September 30,	December 31,
Grant revenues	\$ 1,510	\$ 2,378	\$ —	\$ —
Loss from operations	(8,245)	(9,670)	(12,243)	(15,305)
Net loss	(8,119)	(9,414)	(11,917)	(14,898)
Basic and diluted net loss per common share	\$ (0.49)	\$ (0.46)	\$ (0.54)	\$ (0.62)

## **ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE**

None.

## **ITEM 9A. CONTROLS AND PROCEDURES**

### **Evaluation of Disclosure Controls and Procedures**

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of December 31, 2019, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term “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 the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act are recorded, processed, summarized and reported within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

### **Management’s Annual Report on Internal Control Over Financial Reporting**

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. 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 officer and principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2019. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its 2013 Internal Control – Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2019, our internal control over financial reporting is effective based on those criteria.

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting. For as long as we remain an “emerging growth company” as defined in Section 2(a) of the Securities Act of 1933, or the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, we intend to take advantage of the exemption permitting us not to comply with the requirement that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

### **Changes in Internal Control over Financial Reporting**

There were no changes in our internal control over financial reporting that occurred during the quarter ended December 31, 2019 that have materially affected, or are 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**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2020 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

### **ITEM 11. EXECUTIVE COMPENSATION**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2020 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

### **ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2020 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

### **ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2020 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

### **ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES**

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2020 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

## PART IV

### ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

The following documents are filed as part of this report:

#### 1. Financial Statements

See Index to Financial Statements at Item 8 herein.

#### 2. Financial Statement Schedules

All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

#### 3. Exhibits

Exhibit Number	Description of Document	Incorporate by Reference			Exhibit No.	Filed Herewith
		Form	File No.	Date of Filing		
3.1*	Restated Certificate of Incorporation	S-1/A	333-205001	9/14/2015	3.2	
3.2*	Restated Bylaws	S-1/A	333-205001	9/14/2015	3.4	
4.1*	Form of Common Stock Certificate.	S-1/A	333-205001	9/14/2015	4.1	
4.2*	Amended and Restated Investors' Rights Agreement, dated March 10, 2015, by and among the Registrant and certain of its stockholders, as amended.	S-1	333-205001	6/16/2015	4.2	
4.3*	Amendment #1, dated December 4, 2018, to Amendment and Restated Investors' Rights Agreement, as amended	10-K	001-37722	3/7/2019	4.3	
4.4*	Form of Pre-Funded Warrants	8-K	001-37722	2/7/2019	4.1	
4.5	Description of the Registrant's securities					X
10.1*	Form of Amended and Restated Indemnification Agreement.	10-Q	001-37722	8/9/2018	10.1	
10.2* ‡	2015 Equity Incentive Plan and forms of award agreements.	S-1	333-205001	6/16/2015	10.2	
10.3* ‡	2016 Equity Incentive Plan and forms of award agreements, as amended.	10-Q	001-37722	11/8/2018	10.2	
10.4* ‡	2016 Employee Stock Purchase Plan and forms of award agreements, as amended.	10-K	001-37722	3/7/2019	10.4	
10.5* ‡	2018 Equity Inducement Plan	S-8	333-223614	3/13/2018	99.2	
10.6* ‡	Form of Stock Restriction Agreement.	S-1	333-205001	6/16/2015	10.5	
10.7* ‡	Form of Severance Agreement	8-K	001-37722	4/16/2018	10.1	
10.8* †	Sponsored Research Agreement No. UTA13-001113, dated December 24, 2013, between The University of Texas at Austin ("UT-Austin") and Aeglea BioTherapeutics, Inc., Aeglea Development Company, Inc., AERase, Inc., AEMase, Inc., AECase, Inc., AE4ase, Inc., AE5ase, Inc. and AE6ase., Inc., as amended.	10-Q	001-37722	11/7/2017	10.3	

Exhibit Number	Description of Document	Incorporate by Reference			Filed Herewith
		Form	File No.	Date of Filing	
10.9*	Office Lease, dated November 24, 2014, between Barton Oaks Office Center, LLC and the Registrant.	S-1	333-205001	6/16/2015	10.11
10.10*	First Amendment to Office Lease and Assignment and Assumption of Lease dated September 20, 2016 to Office Lease dated November 24, 2014, between Barton Oaks Office Center, LLC, Aeglea Development Company, Inc., and Aeglea BioTherapeutics, Inc.	10-Q	001-37722	11/9/2016	10.1
10.11* #	Amended and Restated Patent License Agreement No. PM1401501, dated January 31, 2017, between the Registrant and The University of Texas at Austin on behalf of the Board of Regents of the University of Texas system	10-K	001-37722	3/7/2019	10.12
10.12* †	Cancer Research Grant Contract, dated June 15, 2015, between AERase, Inc. and the Cancer Prevention Research Institute of Texas.	S-1	333-205001	6/16/2015	10.15
10.13* ‡	Offer Letter, dated June 16, 2014, issued by the Registrant to Mr. Charles N. York II.	10-K	001-37722	3/23/2017	10.19
10.14* ‡	Offer Letter, dated July 18, 2018, by and between the Registrant and Anthony G. Quinn	8-K	001-37722	7/23/2018	10.1
10.15* ‡	Severance Agreement, dated July 18, 2018, by and between the Registrant and Anthony G. Quinn	8-K	001-37722	7/23/2018	10.2
10.16* #	Master Services Agreement, dated November 26, 2018, between the Registrant, Fujifilm Diosynth Biotechnologies UK Limited, Fujifilm Diosynth Biotechnologies Texas, LLC, and Fujifilm Diosynth Biotechnologies U.S.A, Inc.	10-K	001-37722	3/7/2019	10.18
10.17*	Lease Agreement dated April 30, 2019, between Las Cimas Owner LP and the Registrant	10-Q	001-37722	5/7/2019	10.1
21.1	Subsidiaries of the Registrant.				X
23.1	Consent of independent registered public accounting firm.				X
24.1	Power of Attorney. Reference is made to the signature page hereto.				X
31.1	Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.				X
31.2	Certification of the Principal Financial Officer, pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.				X
32.1(1)	Certification of the Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
32.2(1)	Certification of the Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X



Exhibit Number	Description of Document	Incorporate by Reference			Filed Herewith
		Form	File No.	Date of Filing	
101.INS	XBRL Instance Document.				X
101.SCH	XBRL Taxonomy Extension Schema Document.				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.				X
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document.				X
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document				X

\* Previously filed.

† Confidential treatment has been granted for portions of this exhibit pursuant to Rule 406 of the Securities Act, or Rule 24b-2 of the Exchange Act. The Registrant has omitted and filed separately with the SEC the confidential portions of this exhibit.

‡ Indicates management contract or compensatory plan.

# Registrant has omitted portions of the referenced exhibit and filed such exhibit separately with the Securities and Exchange Commission pursuant to a request for confidential treatment under Rule 24b-2 promulgated under the Exchange Act.

(1) The certifications on Exhibit 32 hereto are deemed not “filed” for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of that Section. Such certifications will not be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act.

#### ITEM 16. FORM 10-K SUMMARY

None.

## SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: February 24, 2020

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Anthony G. Quinn, M.B Ch.B, Ph.D.  
Anthony G. Quinn, M.B Ch.B, Ph.D.  
*President, Chief Executive Officer and Director*  
*(Principal Executive Officer)*

## POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Anthony G. Quinn, M.B. Ch.B, Ph.D. and Charles N. York II, jointly and severally, his or her attorneys-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report on Form 10-K and to file 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 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.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Anthony G. Quinn, M.B Ch.B, Ph.D.</u> Anthony G. Quinn, M.B. Ch.B, Ph.D.	President, Chief Executive Officer and Director (Principal Executive Officer)	February 24, 2020
<u>/s/ Charles N. York II</u> Charles N. York II	Chief Financial Officer and Vice President (Principal Accounting Officer and Principal Financial Officer)	February 24, 2020
<u>/s/ Russell J. Cox</u> Russell J. Cox	Director	February 24, 2020
<u>/s/ Sandesh Mahatme, LLM</u> Sandesh Mahatme, LLM	Director	February 24, 2020
<u>/s/ Armen Shanafelt, Ph.D.</u> Armen Shanafelt, Ph.D.	Director	February 24, 2020
<u>/s/ Suzanne Bruhn, Ph.D.</u> Suzanne Bruhn, Ph.D.	Director	February 24, 2020
<u>/s/ Ivana Magovcevic-Liebisch, Ph.D.</u> Ivana Magovcevic-Liebisch, Ph.D.	Director	February 24, 2020
<u>/s/ Bryan Lawlis, Ph.D.</u> Bryan Lawlis, Ph.D.	Director	February 24, 2020



