

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, DC 20549**

**FORM 10-K**

- ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**  
For the fiscal year ended December 31, 2018
- TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**  
For the transition period from \_\_\_\_\_ to \_\_\_\_\_  
Commission file number 001-37722

**AEGLEA BIOTHERAPEUTICS, INC.**

(Exact name of Registrant as specified in its charter)

Delaware  
(State or Other Jurisdiction of  
Incorporation or Organization)  
901 S. MoPac Expressway  
Barton Oaks Plaza One  
Suite 250  
Austin, TX  
(Address of Principal Executive Offices)

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

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	Name of Each Exchange on Which Registered
Common Stock, \$0.0001 Par Value Per Share	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 if disclosure of delinquent filers pursuant to Rule 405 of Regulation S-K is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definite proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer   
Non-accelerated filer

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, 2018 (the last business day of the Registrant's second fiscal quarter), based upon the closing price of \$10.58 of the Registrant's common stock as reported on The Nasdaq Global Market, was approximately \$199.1 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 March 1, 2019
Common stock, \$0.0001 par value per share	28,819,900 shares

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2019 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2018 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, 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.

**ITEM 1. BUSINESS****Overview**

We are a biotechnology company that designs and develops innovative human enzyme therapeutics for patients with rare genetic diseases and cancer. We believe our novel approach of utilizing human enzymes offers advantages that provide a greater likelihood of clinical success and commercial adoption.

Our drug-hunting capabilities in enzyme engineering, preclinical disease modeling, and drug development in both rare genetic disease and cancer allow us to identify and advance innovative opportunities to address important unmet medical needs for the benefit of patients. Our programs and the decisions we make to progress assets into clinical studies are driven by the following considerations:

- Potential for enhancement of human enzymatic activity
- Ability to create novel human enzymatic activity
- Strong preclinical data and rationale
- Limited or no competition
- Meaningful commercial opportunities
- Worldwide commercial rights

We are a patient-focused organization conscious of the fact that people with a rare genetic disease or cancer have limited treatment options, and we recognize that their lives and well-being are highly dependent upon our efforts to develop improved therapies. For this reason, we are passionate about designing and developing novel therapeutics to address significant unmet medical need for rare genetic disease and cancer.

**Our Strategy**

Our goal is to build a world-class biotechnology company dedicated to the discovery, development, and commercialization of human enzyme-based therapeutics that transform the lives of patients by addressing unmet medical needs in both rare genetic disease and cancer. To achieve that goal, we intend to:

- **Successfully advance our lead product candidate, pegzilarginase, through clinical development.**
- For Arginase 1 Deficiency, we believe we have the only therapeutic in clinical development that addresses the underlying drivers of disease progression. Pegzilarginase is currently being evaluated in two ongoing clinical trials for Arginase 1 Deficiency, consisting of one Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency and one open label extension study for patients with Arginase 1 Deficiency. In December 2018, we announced the design of our global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial with a primary endpoint of plasma arginine reduction and secondary endpoints which include assessments of clinical outcomes on mobility and adaptive behavior, safety and pharmacokinetics. We finalized the design of the PEACE trial to be a single, global pivotal trial based on FDA and EMA feedback. We expect to dose the first patient in the Phase 3 PEACE trial in the second quarter of 2019 and anticipate that topline data from the study will be available in the first quarter of 2021. Additional repeat dose data from our Phase 1/2 clinical trial of pegzilarginase in Arginase 1 Deficiency is expected in the first half of 2019.
- For our oncology indications, pegzilarginase is currently being evaluated in two ongoing clinical trials, consisting of one Phase 1 clinical trial for the treatment of advanced solid tumors, and one Phase 1/2 combination clinical trial of pegzilarginase with Merck's anti-PD-1 therapy, KEYTRUDA® (pembrolizumab) for the treatment of patients with small cell lung cancer (SCLC). After determining the maximum tolerated dose in the Phase 1b combination study, we advanced to Phase 2 in December 2018 and dosed the first patients. We expect that topline data from open label Phase 2 study will be available in the first half of 2020.

- ***Target enzyme-based therapeutic opportunities within rare genetic disease and cancer where regulation of abnormal metabolism provides the potential for important medical benefits.***

Our focus is on rare genetic diseases and cancers where there is a plausible link between disease development, progression, and metabolite levels including amino acids. Advancing to clinical development is gated by strong biological rationale and preclinical data. We favor diseases where there are meaningful potential commercial markets with limited or no current competition and where potential therapy can transform patient outcomes.

- ***Concurrently develop and commercialize multiple product candidates.***

We are committed to the discovery and development of multiple product candidates of engineered human enzymes, as we believe this results in a diversified portfolio, leverages organizational efficiencies, and utilizes economies of scale. This includes continually investing in our internal research capabilities to expand our portfolio.

- ***Develop and implement our precision medicine strategy to increase the probability of clinical success.***

An integral part of our product development programs is a precision medicine strategy designed to identify patient populations for subjects with the greatest potential to benefit from our metabolism focused approaches. In rare genetic disease this strategy is focused on identifying mis-diagnosed and undiagnosed patients. In the United States, we continue to pursue avenues to improve disease state awareness and diagnosis of Arginase 1 Deficiency. In oncology, we are exploring biomarkers to identify patients with tumors sensitive to amino acid deprivation. We believe that targeting these patients will both enhance our ability to detect evidence of clinical activity earlier in clinical development and improve the probability of treating their cancers effectively.

- ***Seek global approval and commercialization of our product candidates.***

We retain worldwide intellectual property rights to all of our product candidates. We intend to pursue clinical and regulatory programs for approval in the United States and internationally. Ultimately, our plan is to establish a multi-country commercial organization in rare genetic disease and seek commercial partnerships in select regional markets. In cancer, we plan to build a focused commercial organization in the United States and strategically evaluate partnership opportunities globally.

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

Our company was initially founded to develop therapeutics for diseases characterized by abnormal amino acid metabolism. We have broadened the scope of our metabolic focus, which we believe allows us to better leverage our enzyme engineering capabilities. 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 and cancer. Our core capability of exploiting these abnormal metabolic pathways has allowed us to develop engineered human enzyme therapies with the potential to reduce toxic levels of amino acids that may lead to novel, disease-modifying treatments for these rare genetic diseases. In addition, with our focus on the innovative field of cancer cell metabolism, we strive to leverage our engineered human enzyme product candidates to degrade the key nutrients needed for cancer cell survival and proliferation. The mechanism of action of our drugs also presents the potential for novel combination therapies when used together with existing or emerging standards of care.

### ***Background on 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, a urea cycle disorder, 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, and death.

There is currently no approved therapeutic agent specifically indicated for Arginase 1 Deficiency or effective treatment options for these patients. Current disease management practice includes a medical diet with protein restriction and ammonia scavengers. 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 reach the range stipulated by medical guidelines. Therefore, this disease management approach is difficult to manage, unpalatable, and generally inadequate to treat the majority of patients. Ammonia-scavenging drugs such as RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylbutyrate) are used to manage elevated ammonia levels. Liver transplantation has been reported to achieve normalization of arginine levels; however, this intervention is available only to a small fraction of patients and carries significant procedural risk.

The lack of a treatment option 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), as well as the accumulation of ammonia caused by the disease related slowing of the urea cycle. The development of an arginine reducing therapeutic introduced early in a patient's life could potentially minimize the exposure to the neurotoxic effects of arginine, its metabolites, and ammonia, as well as potentially enabling improved protein intake. Reduction of plasma arginine levels to below the recommended guidelines 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 established in the medical literature. Newborn screening data for two reliably detected urea cycle disorders allowed disease experts to estimate the incidence of Arginase 1 Deficiency at 1:950,000 births. Assuming a less than normal life span, we believe that at least 600 individuals in global addressable markets have Arginase 1 Deficiency. 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 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 170 patients in the major addressable markets, primarily in the U.S. and Europe.

### **Background on Cancer**

Cancer is the second-leading cause of death in the United States. The National Cancer Institute estimates that in 2018 there were approximately 1.7 million new cases and approximately 610,000 deaths from cancer in the United States. Cancer originates from defects in the cell's genetic code, or DNA, that disrupt the mechanisms that normally prevent uncontrolled cell growth.

We believe that the altered metabolism of cancer cells—the atypical uptake and breakdown of nutrients—provides an opportunity to develop important new cancer treatments. Cancer cells rapidly change how they take up and utilize nutrients. However, while cancer cell metabolic abnormalities fuel tumor growth and alter tumor immune response, they also expose vulnerabilities that can be targeted to selectively destroy tumor cells. It is our belief that depriving cancer cells of key amino acids that are essential for cell survival and tumor growth will provide an effective treatment for some cancers, both as a single agent and in combination with existing or emerging standards of care.

Enzyme-based therapies that degrade amino acids have shown clinical benefit in the treatment of cancer. For example, Oncaspar (pegaspargase) and Erwinaze (asparaginase *Erwinia chrysanthemi*) were approved as part of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia. Degrading the amino acid asparagine with Oncaspar (pegaspargase), an *E. coli*-derived L-asparaginase enzyme, in combination with chemotherapy generates much improved remission rates as compared with chemotherapy alone. Aeglea and other companies have also reported clinical responses with arginine degrading enzyme treatment in some cancers known to be arginine dependent. However, the clinical impact reported by other third parties appear limited as the microbial-derived arginine-degrading enzyme elicited an immune response that appears to neutralize the activity of the drug and therefore may result in limited clinical utility.

The use of microbial enzymes as human therapeutics is often limited by an immune response to a foreign protein. We expect our enzyme product candidates, which are engineered from human proteins, may have more favorable drug-like properties and be less likely to elicit an immune response compared with microbial enzymes. This is supported by our experience with pegzilarginase to date in our clinical programs compared to clinical trials reported in the medical literature with a bacterial-derived arginine depleting enzyme. We believe our approach may provide greater flexibility with respect to the target amino acids that can be addressed.

Using pegzilarginase to enzymatically deplete extracellular arginine needed by some cancer cells provides an approach that, when used alone or in combination with existing or emerging standards of care, has the potential to be an effective treatment paradigm for cancer patients. Published literature suggests that a variety of cancers could potentially respond to amino acid deprivation, which offers us several potential targets for cancer treatment opportunities.

## **Our Development Programs**

### ***Pegzilarginase Overview***

Our lead product candidate, pegzilarginase, is an enhanced human arginase that enzymatically degrades the amino acid arginine. Pegzilarginase is a recombinant, human Arginase 1 enzyme with modifications that enhance the stability and arginine-degrading activity of the enzyme in human plasma, and we believe it may have a lower likelihood of immunogenicity in patients than bacterial arginine-degrading enzymes. Our lead program, pegzilarginase, is in early clinical development for two indications.

1. Arginase 1 Deficiency, which is a rare progressive autosomal recessive metabolic disease caused by a marked decrease in the activity of the native arginase 1 enzyme, which appears to play a key role in the degradation of arginine as part of the urea cycle.
2. Arginine dependent cancers, which demonstrate a potential vulnerability that leads to an increased dependency on extracellular arginine

### ***Pegzilarginase in Rare Genetic Disease***

*PEACE Global Pivotal Phase 3 Study of Pegzilarginase in Patients with Arginase 1 Deficiency:* In December 2018, we announced the design of our single, global pivotal Phase 3 PEACE trial to evaluate the safety and efficacy of pegzilarginase. The trial is believed to be the first-ever investigative therapy that addresses the high arginine levels that are 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 dose the first patient in the PEACE trial in the second quarter of 2019 and anticipate that topline data from the Phase 3 PEACE study will be available in the first quarter of 2021. PEACE is a 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 plasma arginine reduction from baseline. The primary endpoint is intended to assess the effectiveness of pegzilarginase in lowering plasma arginine levels given the evidence that improved 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 mobility and adaptive behavior as assessments of clinically meaningful effects, in addition to safety and pharmacokinetics. 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 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  $\mu$ M.

Patients will be considered eligible for the PEACE trial during screening if they exhibit average plasma arginine of greater than 250  $\mu$ M, are greater than two years of age and have a deficit in at least one dimension of mobility 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 (2 Minute Walk Test or Functional Mobility Assessment) or adaptive behavior (Vineland Adaptive Behavior Scale). 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  $\mu$ M. Additional interim clinical data from our Phase 1/2 clinical trial reporting repeat dose administration of pegzilarginase is expected in the first half of 2019.

*Phase 1/2 Open Label Study of Pegzilarginase in Patients with Arginase 1 Deficiency:* We are conducting 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 is investigating both single ascending doses (Part 1) and repeated dosing (Part 2). The primary endpoint of the trial is safety and tolerability of intravenous administration of pegzilarginase in patients with Arginase 1 Deficiency. The trial also will evaluate the pharmacokinetic and pharmacodynamic effects of repeated doses of pegzilarginase on plasma arginine levels. Additionally, patients who complete the repeat dose part of the Phase 1/2 trial are eligible to enroll in a long-term open label extension study.

In October 2018, we announced new positive interim clinical data at the 2018 American Society of Human Genetics (ASHG) Conference from our ongoing Phase 1/2 trial of pegzilarginase in patients with Arginase 1 Deficiency. We reported clinical improvements with repeat dose administration of pegzilarginase after only eight weeks, including consistent reduction of arginine and improvement in mobility or adaptive behavior. Pegzilarginase was generally well tolerated; most treatment-related adverse events were mild, and while investigators considered some of the hypersensitivity events as serious adverse events, they were generally manageable with standard measures and all patients continued study treatment. Additionally, we completed and exceeded our enrollment target with 16 patients in the Phase 1/2 clinical trial.

If the data from our Phase 1/2 and open label extension trials are supportive, we may seek to accelerate our development plan for pegzilarginase by requesting to use established regulatory pathways, such as Breakthrough Therapy Designation. Regardless of whether we receive this designation, we anticipate initiating a pivotal trial in the second quarter of 2019 and, if successful, we expect that this trial would support registration filing in the US and Europe.

*Phase 1/2 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 are 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 December 2017, we announced the initiation of this study with the recruitment of two patients who had previously completed the repeat dose phase (Part 2) of the previous study. Currently, 10 patients have enrolled in the long-term open label extension study, and we expect to enroll 13 patients by the second quarter of 2019.

*Regulatory Designations:* We have obtained orphan drug designation from the FDA and EMA, as well as Fast Track Designation from the FDA, for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. In addition, we announced in October 2018 that 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.

### ***Pegzilarginase in Cancer***

*Background Biology:* We are developing pegzilarginase to target arginine-dependent cancers. Arginine is considered a semi-essential amino acid because, under conditions such as enhanced proliferation, tissue injury, or stress, cells are unable to make enough arginine and are therefore dependent on an extracellular source. The role of arginine and its metabolites in cancer has been studied extensively in preclinical models with demonstrated effects, including enhancement of tumor growth and cellular proliferation. Conversely, restriction of dietary arginine attenuates tumor growth in experimental tumor models.

Many types of cancers lack the ability to synthesize intracellular arginine due to lack of expression of argininosuccinate synthase1 (ASS1), argininosuccinate lyase (ASL), or ornithine transcarbamoylase (OTC), which are enzymes in the urea cycle. As a result, these cancers depend on extracellular arginine without which they may exhibit reduced protein synthesis and proliferation, and undergo autophagy and/or apoptosis, establishing a correlation between their inability to synthesize arginine and vulnerability to arginine deprivation. Based on data from our preclinical studies and the published scientific and medical literature, arginase 1 degrades arginine to ornithine and urea. Ornithine cannot be used to make arginine by cancer cells that lack expression of OTC, ASS or ASL. Pegzilarginase is intended to target cancer cells that depend on extracellular arginine by depriving the cells of the amino acid that is essential for cell survival and tumor growth. We believe pegzilarginase has the potential to provide an effective treatment option in combination with existing or emerging standards of care for patients with some cancers.

*Diagnostic Potential:* As documented in scientific and medical literature and from our own preclinical research, the lack of expression of any one or more of the enzymes OTC, ASS1 or ASL in tumor cells has been shown to be associated with cancer cell sensitivity to arginine depletion. Our preclinical research has focused on the reduction or loss of expression of ASS1 as the predominant cause of tumor arginine dependence. We found that low or no expression of ASS1 in nonclinical patient derived xenograft models of melanoma or SCLC can result in sensitivity to arginine depletion by pegzilarginase.

*Phase 1/2 Combination Trial in Patients with SCLC:* In the first quarter of 2018, we initiated an open label Phase 1b clinical collaboration with Merck to evaluate the combination of pegzilarginase with Merck's anti-PD1 therapy, pembrolizumab, for the treatment of patients with SCLC that relapsed or progressed after platinum-based chemotherapy. The primary objectives in Phase 1b were to determine the safety and recommended dose of pegzilarginase to be used in combination with pembrolizumab in Phase 2. In March 2019, we announced the Phase 1b topline data from 16 patients enrolled across three cohorts. The recommended Phase 2 dose was established at 0.27 mg/kg/week of pegzilarginase in combination with pembrolizumab. Of nine patients in Phase 1b treated at the recommended Phase 2 dose, three patients had stable disease at 9 weeks, one partial response was observed, and three patients remained on treatment as of the data cutoff. The safety profile was consistent with pegzilarginase monotherapy observations.

We initiated enrollment in open label Phase 2 in December 2018 with topline data expected in the first half of 2020. The Phase 2 primary objective is objective response rate (ORR), and secondary objectives include safety, clinical benefit rate, time to response, duration of response, progression free survival (PFS), and overall survival.

*Phase 1 Dose Escalation Trial of Pegzilarginase in Patients with Advanced Solid Tumors:* In October 2015, we initiated the Phase 1 open label, multiple dose, dose escalation clinical trial in patients with advanced solid tumors. The primary objective of dose-escalation is to determine the maximum tolerated dose, and secondary objectives are to evaluate the safety, tolerability, and pharmacokinetic profile of pegzilarginase. The inclusion criteria include 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.

In December 2017, we reported topline results of the dose escalation trial in which 40 patients were enrolled. The maximum tolerated dose was established at 0.33 mg/kg weekly by intravenous infusion, based on observations of reversible rash and reversible tremor at 0.40 mg/kg/week. Two dose-limiting toxicities (DLT) were observed: failure to thrive and maculopapular rash. Other treatment-related serious or Grade 3/4 adverse events (AEs) that were not DLTs per protocol, including those that occurred after the DLT window, were hypophosphatemia, anemia (developed from a Grade 1 baseline), neutropenia (developed from a Grade 1 baseline), tremor, weakness, and transient hypertension. Treatment-related AEs in 10% or more of patients included nausea, stomatitis/mouth sores, fatigue, vomiting, rash, decreased appetite, and diarrhea, which were primarily Grades 1 or 2. Other serious adverse events, including death, occurred on study but were not considered related to pegzilarginase treatment. Most patients discontinued due to disease progression, and only one patient discontinued due to an adverse event that was considered related to pegzilarginase (tremor). Clinical proof of mechanism was demonstrated, with a rapid and sustained reduction of plasma arginine to levels substantially less than the normal range in cancer patients. Additionally, preliminary evidence suggesting clinical activity was observed in two patients with forms of melanoma who had stable disease longer than 12 weeks while receiving pegzilarginase.

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 suggested that a significant fraction of patients are expected to have cancers that are dependent on extracellular arginine. The primary endpoint of each cohort expansion is to assess the safety of pegzilarginase in patients with each tumor type. Secondary endpoints include the assessment of pharmacokinetics, pharmacodynamics and clinical response. We plan to also use the data to inform the viability of companion diagnostic development, which has the potential to enrich patient populations with the greatest likelihood of clinical success.

In March 2019, we announced the completion of enrollment to three separate cohort expansions of patients with heavily pre-treated SCLC, uveal melanoma, and cutaneous melanoma, with clinical data expected to be submitted for publication later in 2019. We previously presented interim clinical data at the European Society for Medical Oncology (ESMO) 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. The results, combined with preclinical evidence of synergy with immune checkpoint inhibitors, support further clinical evaluation of pegzilarginase in immunotherapy combinations.

## **Preclinical Pipeline**

### ***AEB4104 in Patients with Homocystinuria***

AEB4104 is a novel recombinant human enzyme that degrades the amino acid homocysteine and its oxidized form homocystine. Aeglea is developing AEB4104 for the treatment of patients with cystathionine beta synthase (CBS) deficiency, also known as Classical Homocystinuria.

Homocystinuria is an inherited disorder of methionine metabolism caused by mutations in CBS and other genes leading to elevated levels of plasma and tissue homocysteine and homocystine, which affect multiple organ systems and cause early mortality. Current disease management, which includes dietary protein (methionine) restriction, vitamins, and betaine supplementation, is insufficient to effectively control the more severe forms of the disease.

In October 2018, we announced preclinical efficacy data on our AEB4104 homocystinuria program at the 2018 American Society of Human Genetics (ASHG) Conference, demonstrating that AEB4104 improved survival and correction of disease-related abnormalities in a preclinical model of homocystinuria. AEB4104 decreased homocysteine and homocystine levels in the plasma, including the cystathionine beta synthase (CBS) deficient model (CBS<sup>-/-</sup>) and the high methionine diet-induced model of homocystinuria. Treatment with AEB4104 prevented early mortality, stopped disease progression, and reversed liver pathology in the cystathionine beta synthase (CBS) deficient model (CBS<sup>-/-</sup>).

We believe homocystinuria represents a viable market opportunity with significant unmet medical need, which we plan to address by continuing our preclinical development of AEB4104. Given the severity of the disease, the limitations of current disease management approaches, and the data demonstrating improved survival in a preclinical model of the disease, Aeglea initiated IND-enabling activities and is progressing manufacturing, pharmacology and other activities to support preclinical toxicology studies and advancement towards clinical trials. We anticipate filing an IND or CTA in the first quarter of 2020.

### ***AEB5100 in Patients with Cystinuria***

AEB5100 is a novel recombinant human enzyme that degrades plasma cystine and cysteine. Aeglea is developing AEB5100 for the treatment of patients with cystinuria, 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.

In October 2018, we announced preclinical efficacy data on our AEB5100 cystinuria therapeutic program at the 2018 American Society of Nephrology (ASN) Conference, demonstrating that AEB5100 lowered blood levels of cystine, decreased the amount of cystine in the urine and reduced both cystine crystal and kidney stone formation in a preclinical model of cystinuria. Given the compelling preclinical data and the limitations of current disease management approaches, Aeglea initiated IND-enabling activities and is progressing manufacturing, pharmacology and other activities to support preclinical toxicology studies and advancement towards clinical trials. We anticipate filing an IND or CTA in the second half of 2020.

### **AEB3103**

AEB3103 is an engineered human enzyme that targets the degradation of the amino acid cysteine/cystine. Initial efficacy testing in preclinical models demonstrated significant depletion of glutathione and significantly increased levels of ROS in HMVP2 prostate cancer cells.

### **AEB2109**

AEB2109 is an engineered human enzyme that targets the degradation of the amino acid methionine. Earlier work from our enzyme engineering program has been presented in the scientific literature describing activity in an animal tumor model. We believe AEB2109 provides us with the opportunity to exploit a tumor vulnerability not yet successfully exploited for therapeutic benefit. We plan to continue our preclinical development efforts for AEB2109 and, if appropriate, proceed to IND-enabling studies with a development candidate from this program.

### **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.

As of December 31, 2018, we are the owner of seven U.S. patents, expiring between 2029 and 2032, absent any extensions; three patents of which are directed to the compositions or methods of preparing pegzilarginase, and three patents of which are directed to compositions of methionine-gamma lyase enzymes, methods of treatment using the enzymes, nucleic acids encoding the enzymes, or methods of identifying the enzymes. One U.S. patent is to arginase variants other than pegzilarginase. As of December 31, 2018, we are the owner of three U.S. patent applications that include methods of treatment that can use pegzilarginase. As of December 31, 2018, we are the owner of one U.S. patent application that includes methionine-gamma-lyase enzymes that can include AEB2109 having L-methionine degrading activity. As of December 31, 2018, we are also the owner of three pending U.S. patent provisional applications that include methods of treatment that can use pegzilarginase.

As of December 31, 2018, we also controlled two U.S. patents and five U.S. patent applications, exclusively licensed to us by the Board of Regents of The University of Texas System, or the University. The two U.S. patents include compositions, methods of treatment, or nucleic acids encoding the compositions that include AEB2109. One U.S. patent application is directed to cystathionine-gamma-lyase variants other than AEB2109. One U.S. patent application is directed to a method of treatment that include using AEB2109. Three of the U.S. patent applications include compositions or methods of treatment that include AEB3103. One U.S. application includes enzyme variants and methods of treatment using the enzyme variants that can include AEB4104. As of December 31, 2018, we also controlled one U.S. provisional patent application that includes compositions that include AEB5100. Any patents and patents issuing from the foregoing licensed U.S. patent applications are expected to expire between 2034 to 2038, absent any adjustments or extensions.

As of December 31, 2018, we owned a total of eight patents and five patent applications in foreign jurisdictions variously including: Australia, Canada, China, Europe, Japan, Hong Kong, Taiwan, and South Korea. As of December 31, 2018, we are the owner of two PCT applications. Any issued foreign patents or patents issuing from these foreign patent applications, are expected to expire between 2029 and 2038, absent any adjustments or extensions. These owned foreign patent applications and patents include compositions of pegzilarginase or methods of using pegzilarginase to treat cancer or arginine 1 deficiency, or compositions and methods of using methionine-gamma-lyase enzyme variants. As of December 31, 2018, we also controlled one Europe patent, three PCT applications, and thirteen pending foreign patent applications in Australia, Canada, China, Europe, Israel, Japan and South Korea, which are also exclusively licensed to us by the University. The controlled foreign Europe patent includes cystathionine-gamma-lyase variants, their formulations and use in treatment in cancer and includes AEB2109. The controlled foreign patent applications include compositions and their use in treatment that can include AEB2109 or AEB3103. One PCT application includes compositions that can include AEB4104. Any foreign patent and foreign patents issuing from these controlled foreign applications are expected to expire between 2034 and 2038, absent any adjustments or extensions.

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 use other forms of protection, such as trademark, copyright and trade secret protection, to protect our intellectual property, particularly where we do not believe patent protection is appropriate or obtainable. 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.

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, 2018, we have paid \$0.1 million under these license agreements.

In connection with the above license agreements, we and each of our wholly-owned subsidiaries also entered into a Sponsored Research Agreement, or SRA, with the University on December 24, 2013, which was subsequently amended. Pursuant to the SRA, we agreed to sponsor research to be conducted at the laboratory of Professor George Georgiou at the University related to the systemic depletion of amino acids for cancer therapy, and enzyme replacement for the treatment of patients having inborn metabolic defects. The SRA expired on August 31, 2018. For the year ended December 31, 2018, we paid \$0.2 million to the University under the SRA.

## **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 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 and cancer.

**Rare genetic disease.** With respect to pegzilarginase for Arginase 1 Deficiency, there are currently no approved therapeutics 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 medical management of 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.

**Cancer.** With respect to our oncology product candidates, we compete with other companies that pursue a cancer metabolism approach, as well as companies that employ more common methods of treating patients such as surgery, radiation and drug therapy. These drug therapies include chemotherapy, hormone therapy and targeted drugs, including biologic products such as engineered antibodies.

There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. Our product candidates may compete with many such therapies whether used in combination with or as an adjunct to other cancer therapies. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors. In general, although there has been considerable progress over the past few decades in the treatment of cancer and the currently marketed therapies provide benefits to many patients, most of these therapies are limited to some extent in their efficacy and frequency of adverse events, and none are successful in treating all patients. As a result, the level of morbidity and mortality from cancer remains high.

In addition to currently marketed therapies, there are also a number of medicines in late-stage clinical development to treat cancer. While there are currently no approved drugs targeting tumor arginine dependence, we are aware of a number of compounds that are in clinical development and enrolling patients with solid and hematological malignancies, including Polaris Group's microbial ADI-PEG 20 and Athenex's pegylated native human arginase 1. Additionally, Calithera Biosciences is targeting a therapy that inhibits arginase 1 as an immune modulator. These medicines in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for our product candidate pegzilarginase.

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 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 as the compound progresses through clinical development, prior to seeking marketing approval from FDA. We believe we have sufficient supplies of pegzilarginase for our ongoing and currently expected Phase 1/2 clinical trial to evaluate the combination of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer and the Phase 3 pivotal trial in conjunction with the open label extension study for the treatment of patients with Arginase 1 Deficiency.

### ***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. Beginning in fiscal year 2018, this annual program fee replaces the annual product and established fees. 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 regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

### ***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 the potential to substantially change healthcare financing and delivery by both governmental and private insurers, and significantly impact the pharmaceutical and biotechnology industry. The ACA will impact existing government healthcare programs and will result 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 50% point-of-sale discounts (increased to 70% beginning in 2019) 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.

We anticipate that the ACA will result in additional downward pressure on coverage and the price that we receive for any approved product, and could seriously harm our business. Any reduction in reimbursement from Medicare and 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 products.

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 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, 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, 2018, we had a total of 61 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, 2018, 2017 and 2016 and our total assets as of December 31, 2018 and 2017, 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 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 any clinical trials, including large-scale, pivotal clinical trials, 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 little experience in conducting clinical trials. In part because of this lack of 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. We have no approved products and have only begun clinical development of pegzilarginase. 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, 2018, 2017, and 2016, we reported a net loss of \$44.3 million, \$27.2 million and \$21.7 million, respectively. As of December 31, 2018, we had an accumulated deficit of \$116.9 million. We have financed our operations primarily through private placements of our preferred stock, the initial public offering, or IPO, 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 only conducting clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency and advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab. We have not initiated clinical development of our other product candidates and expect that it will be many years, if ever, before we have a product candidate 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 only conducting clinical development for pegzilarginase for the treatment of Arginase 1 Deficiency and advanced solid tumors, as well as a combination clinical trial of pegzilarginase with pembrolizumab and are only 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 currently conducting multiple clinical trials for pegzilarginase, consisting of one Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency, one Phase 1 clinical trial for the treatment of patients with advanced solid tumors with multiple cohort expansions, and one Phase 1/2 clinical trial to evaluate the combination of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer. We have initiated the planned expansion cohorts of our Phase 1 trial of pegzilarginase for the treatment of advanced solid tumors to study small cell lung cancer, uveal melanoma, and cutaneous melanoma, and each of these histologies has been shown in published literature and preclinical studies to demonstrate a dependence on arginine in a substantial proportion of tumors. If our product candidate fails to work as we expect, or if we need to conduct additional studies to better understand the relationship between our product candidate 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 (AML) and myelodysplastic syndrome (MDS) in December 2017 due to lack of evidence of clinical benefit. Also, while there is an established link between seizures and elevated levels of certain arginine metabolites, we may not be able to determine the relationship between clinical activity and arginine and its metabolites, if any, for the treatment of Arginase 1 Deficiency. Any such events may result in longer development times, larger trials and a greater likelihood of terminating the trial or not obtaining regulatory approval.

In addition, as 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, including pegzilarginase, in clinical trials specific for a given tumor type and this will result in increased time and cost. Even if our product candidate demonstrates efficacy in a particular tumor type, we cannot guarantee that any product candidate, including pegzilarginase, will behave similarly in all tumor types, and we will be required to obtain separate regulatory approvals for each tumor type we intend a product candidate to treat. If any of our ongoing or planned clinical trials are unsuccessful, our business will suffer.

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

In developing a product candidate, we expect that if we use a biomarker-based test in cancer trials to identify and only enroll patients in clinical trials with tumors that express the biomarker, the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate. 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. EMA, MHRA or comparable foreign regulatory authorities may also 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 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 discovery 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 in connection with 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, and marketable securities as of December 31, 2018, in conjunction with the net proceeds received from our public offering in February 2019, we estimate such funds will be sufficient for us to fund completion of our global pivotal Phase 3 PEACE clinical trial and ongoing Phase 1/2 trial for the treatment of patients with Arginase 1 Deficiency, our ongoing Phase 1 clinical trial for the treatment of patients with advanced solid tumors, as well as our ongoing Phase 1/2 combination clinical trial of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer. 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 other than our grant agreement with the Cancer Prevention and Research Institute of Texas, or CPRIT, which ended on May 31, 2018. As of December 31, 2018, the full \$19.8 million of grant proceeds had been collected. 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. All of our product candidates, other than pegzilarginase, are still in nonclinical development or nonclinical testing, and for pegzilarginase, the early stages of clinical development. 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 advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab in patients with small cell lung cancer. 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 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;
- 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 these ongoing clinical trials or in future 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 have announced interim data from our ongoing clinical trials of pegzilarginase for the treatment of Arginase 1 Deficiency and advanced solid tumors, such reports were 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 weeks of dosing may not be representative of our observations with subsequently dosed patients out to eight weeks or longer. We have announced the design of our single, global pivotal Phase 3 PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) trial to evaluate the safety and efficacy of pegzilarginase. We expect to dose the first patient in the PEACE trial in the second quarter of 2019 and anticipate that data from the Phase 3 PEACE study will be available in the first quarter of 2021. Furthermore, our ongoing Phase 1/2 clinical trial for the treatment of patients with Arginase 1 Deficiency and our Phase 1 clinical trials for the treatment of advanced solid tumors will primarily evaluate the safety of our product candidates. Moreover, 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. 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, in March 2018, a pediatric patient previously dosed in Part 1 of 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 with Arginase 1 Deficiency or patients with tumors, including the identification of patients with Arginase 1 Deficiency or development or identification of a test, if needed, to screen for those cancer patients;
- 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 screen for patients with tumors dependent on arginine that pegzilarginase is designed to target and with 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 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 announced the design of our global pivotal Phase 3 PEACE trial in which we intend to study plasma arginine reduction from baseline as our primary endpoint. However, evidence of stabilization or improvement of clinical signs and symptoms of Arginase 1 Deficiency, such as our secondary endpoints with the assessment of clinical outcomes on mobility and adaptive behavior, as well as clinician and caregiver global impressions of effectiveness, may be required in addition to the primary endpoint to support approval. We may face difficulties or delays in enrolling our Phase 3 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 longer duration dosing may increase the likelihood of seeing changes in clinical outcomes. 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 and advanced solid tumors, including a combination clinical trial of pegzilarginase with pembrolizumab. 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. 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 for our oncology indications represent a novel approach to cancer treatment, 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 early-stage 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 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 advanced solid tumors, as well as a 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. In a Phase 1 trial of pegzilarginase for the treatment of patients with advanced solid tumors and a previously concluded trial of pegzilarginase for the treatment of the patients with hematological malignancies AML and MDS, we have observed serious adverse events in some patients, including death. In 2018, we 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 manifested as acute agitation. In October 2018, we announced updated interim clinical data from our ongoing Phase 1/2 trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency, in which we observed 4 hypersensitivity events of at least moderate severity that were considered related to the administration of pegzilarginase in 3 patients. Three of these hypersensitivity events were considered by investigators as serious adverse events. These hypersensitivity events were due to the development of anti-drug antibodies to pegzilarginase. Hypersensitivity reactions and immunogenicity manifest as anti-drug antibodies could impact the safety and efficacy of pegzilarginase. 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 some patients who lack the target enzyme, as is the case with patients with Arginase 1 Deficiency that we are treating in our Phase 1/2 trial, open label extension study, and our future trials 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 pegzilarginase to be 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, 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. Newborn screening data for two reliably detected urea cycle disorders allowed disease experts to estimate the incidence of Arginase 1 Deficiency at 1:950,000 births. Assuming a less than normal life span, we believe that at least 600 individuals in global addressable markets have Arginase 1 Deficiency. Presently, only 34 U.S. states and jurisdictions screen for Arginase 1 Deficiency, and screening in Europe is not universal. 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 pediatric patients may be eligible for inclusion in our planned global pivotal Phase 3 trial. To date, we have identified more than 170 patients in the global addressable markets, primarily in the U.S. and Europe.

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 Pharma plc has gained approval for its products 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 effect of their condition by taking RAVICTI (glycerol phenylbutyrate) or through dietary protein restriction. 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 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 currently conducting a 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. These 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. Although Merck has agreed to provide pembrolizumab in connection with our ongoing combination trial, 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 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 alone, or result in new side effects that have not previously been identified with pegzilarginase 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 landscape 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 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.

***The market opportunities for our product candidates may be limited to those patients who are ineligible for or have failed prior treatments.***

Cancer therapies are sometimes characterized as first-line, second-line or third-line based on the order they should be used in relation to other products, and the FDA often approves new therapies initially only for third-line use. Initial approvals for new cancer therapies are often restricted to later lines of therapy for patients with advanced or metastatic disease, limiting the number of patients who may be eligible for such new therapies, which may include our product candidates.

***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 who have advanced solid tumors dependent on arginine, as well as the potential subset of those who have the potential to benefit from treatment with our product candidates such as pegzilarginase, 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. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and physicians may continue to rely on these treatments instead of adopting the use of pegzilarginase for the treatment of patients with arginine dependent cancers. In addition, many new drugs have been recently approved and many more are in the pipeline to treat patients with cancer. Additionally, current treatments for Arginase 1 Deficiency include dietary protein restriction and, 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 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. For example, Horizon Pharma plc has gained approval for its drug RAVICTI (glycerol 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. We also face intense competition from companies developing products and therapies to treat cancer. For example, Polaris Group is conducting numerous clinical trials of ADI-PEG 20, an enzyme derived from mycoplasma, which degrades arginine in the blood.

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, 2018, had only 61 employees, including four 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 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 original branded product is approved 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.

We believe that if any of our product candidates are approved as a biological product under a BLA, it should qualify for the 12-year period of exclusivity. However, there is a risk that the FDA will not consider any of our product candidates to be reference products for competing products, 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. Moreover, the extent to which a 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. 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 and pipeline product candidates. We also expect to continue to rely on such third parties to manufacture and supply commercial quantities of pegzilarginase. In addition, we rely on Merck to provide pembrolizumab for the conduct of our combination trials.

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 for oncology indications 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 in oncology 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, 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. 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 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.

Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

***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 do not currently have Breakthrough Therapy Designation for any of our product candidates, but may seek such designation. 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. In any event, the receipt of a Breakthrough Therapy designation for a product candidate may not result in a faster development process, review or approval compared to drugs or biologics considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our 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 products 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. The information was made publicly available on a searchable website in September 2014 and is disclosed 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. 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 (GDPR) took effect in the European Economic Area (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. 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.***

The U.S. government has recently 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 newly enacted 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. For example, India does not allow patents for methods of treating the human body or medical use claims as in other jurisdictions. 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 many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, in some cases we 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. For example, unlike other countries, China has a heightened requirement for patentability and specifically requires a detailed description of medical uses of a claimed therapeutic. 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 in Europe and certain developing countries, including India and China, 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 a number of 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 particular, we partner with the University of Texas at Austin, which is a U.S. academic institution, in order to accelerate our discovery and nonclinical development work under a Sponsored Research Agreement.

The University of Texas at Austin has provided us with an option to negotiate a royalty-bearing, exclusive license to any invention or discovery that is conceived or reduced to practice during the term of the Sponsored Research Agreement. Regardless of such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue a program based on that technology.

In December 2013, our wholly-owned subsidiaries AECCase, 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 product candidates AEB3103 and AEB2109. In January and December 2017, we and the University of Texas at Austin entered into and subsequently amended an Amended and Restated Patent License Agreement which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us, or the Restated License. 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 U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products, and recent patent reform 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 and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the 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.

For our U.S. patent applications containing a claim not entitled to priority before March 16, 2013, there is a greater level of uncertainty in the patent law. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, which affect both the way patent applications will be prosecuted and potentially patent litigation. The U.S. PTO has promulgated regulations and developed procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act (in particular, the first to file provisions) did not come into effect until March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our 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.

An important change introduced by the Leahy-Smith Act is that, as of March 16, 2013, the United States transitioned to a "first-to-file" system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the U.S. PTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Furthermore, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our technology and the prior art allow our technology to be patentable over the prior art. 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.

Among some of the other changes introduced by the Leahy-Smith Act are changes that limit where a patentee may file a patent infringement suit and that allow third parties to challenge any issued patent, whether issued before or after March 16, 2013, in the U.S. PTO. Because of a lower evidentiary standard in U.S. PTO proceedings compared to the evidentiary standard in United States federal court necessary to invalidate a patent claim, a third party could potentially provide evidence in a U.S. PTO proceeding sufficient for the U.S. PTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the U.S. PTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action.

***If we do not obtain patent term extensions in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially 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 under the Hatch-Waxman Act. The Hatch-Waxman Act 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 majority of our capital stock as of December 31, 2018. As a result, if these stockholders were to choose to act together, they would 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 beginning with the year ended December 31, 2017. 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, 2020. 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 have been required to furnish a report by our management on our internal control over financial reporting beginning with the year ending December 31, 2017. 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**

Our corporate headquarters occupy approximately 10,100 square feet of leased office space in Austin, Texas pursuant to a lease that expires in 2020. In October 2018, we amended and extended a separate lease agreement for approximately 4,560 square feet of laboratory space in Austin, Texas, which will expire in September 2021. 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.

**ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES**

**Market Information and Holders**

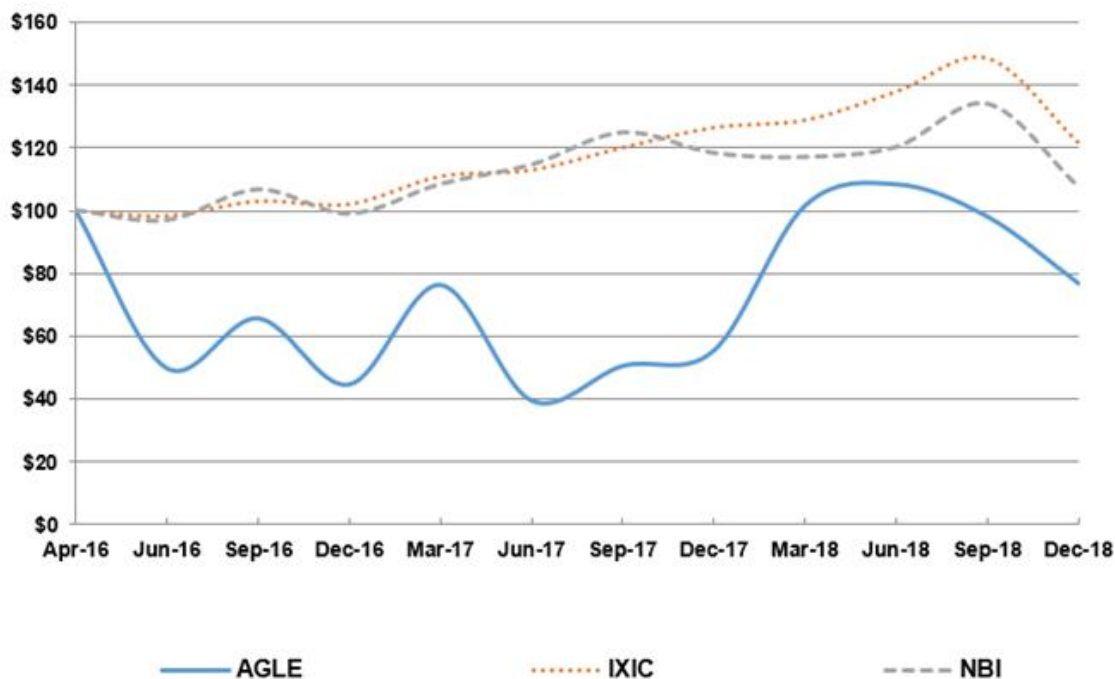
Our common stock is traded on The Nasdaq Global Market under the symbol "AGLE."

**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, 2018. 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
Aeglea Biotherapeutics, Inc.	AGLE	\$ 100.00	\$ 44.52	\$ 55.37	\$ 76.66
Nasdaq Composite Index	IXIC	\$ 100.00	\$ 102.12	\$ 126.43	\$ 121.42
Nasdaq Biotechnology Index	NBI	\$ 100.00	\$ 98.88	\$ 118.33	\$ 107.34

#### 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.

**Use of Proceeds from Registered Securities**

On April 6, 2016, our Registration Statement on Form S-1 (File No. 333-200501) relating to the IPO of our common stock was declared effective by the SEC.

There has been no material change in our planned use of the net proceeds from the IPO, as described in our final prospectus filed with the SEC on April 7, 2016.

**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, 2018, 2017, and 2016, and the balance sheet data as of December 31, 2018 and 2017 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, 2015 and 2014 and the balance sheet data as of December 31, 2016, 2015, and 2014 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,				
	2018	2017	2016	2015	2014
(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	36,719	22,815	18,143	11,453	6,830
General and administrative	12,632	10,066	8,391	5,947	2,074
Total operating expenses	<u>49,351</u>	<u>32,881</u>	<u>26,534</u>	<u>17,400</u>	<u>8,904</u>
Loss from operations	(45,463)	(27,676)	(21,906)	(11,315)	(8,904)
Other income (expense):					
Interest income	1,172	482	244	22	1
Change in fair value of forward sale contract	—	—	—	-	(1,444)
Other expense, net	(57)	(42)	(36)	(2)	—
Total other income (expense)	<u>1,115</u>	<u>440</u>	<u>208</u>	<u>20</u>	<u>(1,443)</u>
Net loss	(44,348)	(27,236)	(21,698)	(11,295)	(10,347)
Deemed dividend to convertible preferred stockholders	—	—	—	(228)	—
Net loss attributable to common shareholders and stockholders	<u>\$ (44,348)</u>	<u>\$ (27,236)</u>	<u>\$ (21,698)</u>	<u>\$ (11,523)</u>	<u>\$ (10,347)</u>
Common Stock:					
Net loss per share, basic and diluted	\$ (2.13)	\$ (1.80)	\$ (2.22)	\$ (19.21)	\$ —
Net loss attributable to common stockholders	\$ (44,348)	\$ (27,236)	\$ (21,698)	\$ (11,523)	\$ —
Weighted-average common shares outstanding, basic and diluted	20,822,560	15,128,192	9,791,728	599,788	—
Class A-1 common:					
Net loss per share, basic and diluted	\$ —	\$ —	\$ —	\$ —	\$ (20.13)
Net loss attributable to class	\$ —	\$ —	\$ —	\$ —	\$ (3,321)
Weighted-average common shares outstanding, basic and diluted	—	—	—	—	165,000
Class A common:					
Net loss per share, basic and diluted	\$ —	\$ —	\$ —	\$ —	\$ (17.06)
Net loss attributable to class	\$ —	\$ —	\$ —	\$ —	\$ (5,706)
Weighted-average common shares outstanding, basic and diluted	—	—	—	—	334,522
Class B common:					
Net loss per share, basic and diluted	\$ —	\$ —	\$ —	\$ —	\$ (40.17)
Net loss attributable to class	\$ —	\$ —	\$ —	\$ —	\$ (1,320)
Weighted-average common shares outstanding, basic and diluted	—	—	—	—	32,861

	As of December 31,				
	2018	2017	2016	2015	2014
	(in thousands)				
<b>Consolidated Balance Sheet Data:</b>					
Cash, cash equivalents, and marketable securities	\$ 74,513	\$ 50,299	\$ 63,502	\$ 33,062	\$ 2,616
Working capital	66,432	49,362	62,459	35,763	1,672
Total assets	77,739	56,077	67,063	38,654	2,930
Total liabilities	10,311	5,740	4,097	2,550	1,058
Convertible preferred shares	—	—	—	58,311	13,345
Accumulated deficit	(116,861)	(72,513)	(45,277)	(23,579)	(12,284)
Total members'/stockholders' equity (deficit)	67,428	50,337	62,966	(22,207)	(11,473)

## 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 biotechnology company that designs and develops innovative human enzyme therapeutics for patients with rare genetic diseases and cancer. We believe our novel approach of utilizing human enzymes offers advantages that provide a greater likelihood of clinical success and commercial adoption.

Our drug-hunting capabilities in enzyme engineering, preclinical disease modeling, and drug development in both rare genetic disease and cancer allow us to identify and advance innovative opportunities to address important unmet medical needs for the benefit of patients. Our programs and the decisions we make to progress assets into clinical studies are driven by the following considerations:

- Potential for enhancement of human enzymatic activity
- Ability to create novel human enzymatic activity
- Strong preclinical data and rationale
- Limited or no competition
- Meaningful commercial opportunities
- Worldwide commercial rights

We are a patient-focused organization conscious of the fact that people with a rare genetic disease or cancer have limited treatment options, and we recognize that their lives and well-being are highly dependent upon our efforts to develop improved therapies. For this reason, we are passionate about designing and developing novel therapeutics to address significant unmet medical need for rare genetic disease and cancer.

Our lead product candidate, pegzilarginase, is engineered to degrade the amino acid arginine and is being developed to treat two extremes of arginine metabolism, including arginine excess in patients with Arginase 1 Deficiency, a rare genetic disease, as well as some cancers which have been shown to have a metabolic dependence on arginine. Pegzilarginase is being evaluated in multiple ongoing clinical trials and we expect to start a single, global pivotal Phase 3 trial in patients with Arginase 1 Deficiency in the second quarter of 2019. Currently our development consists of a Phase 1/2 clinical trial for the treatment of Arginase 1 Deficiency, an open label extension study for patients with Arginase 1 Deficiency, a Phase 1 clinical trial for the treatment of advanced solid tumors, and a Phase 1/2 combination clinical trial of pegzilarginase with pembrolizumab for the treatment of patients with small cell lung cancer (SCLC). We are also building a pipeline of additional product candidates targeting key amino acids and other metabolites, including AEB4104 for the treatment of homocystinuria, AEB5100 for the treatment of cystinuria, and AEB3103 and AEB2109 for the treatment of cancer.

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, or IPO, 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 \$44.3 million, \$27.2 million, and \$21.7 million for the years ended December 31, 2018, 2017, and 2016, 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, 2018, we had an accumulated deficit of \$116.9 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 and diagnostic development activities for our lead product candidate, pegzilarginase; concurrently develop our pipeline product candidates; 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, most notably, our lead product candidate pegzilarginase. Although we opened an internal research laboratory in February 2017, we continue to 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, operations, and human resources functions. Other significant costs include legal fees relating to corporate matters and fees for insurance, accounting, consulting, 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, and marketable securities.

### **Income taxes**

We serve as a holding company for our seven wholly-owned 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 and stock-based compensation.

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.

### ***Stock-based compensation***

We recognize the cost of stock-based awards granted to 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. We elected to early adopt ASU 2018-07, *Compensation – Stock Compensation (Topic 718)* effective January 1, 2018. All non-employee share-based payment awards granted prior to adoption were remeasured at fair value as of the adoption date. There was no material impact on our consolidated financial statements from the adoption. All non-employee share-based payment awards granted after adoption are measured at grant-date fair value. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable.

We estimate the grant date fair value of stock options granted using the Black-Scholes option-pricing model, which requires the use of highly subjective assumptions to determine the fair value of the awards. These assumptions include:

- *Expected term* – The expected term represents the period that the 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).
- *Expected volatility* – Since we have only been publicly traded for a short period and do not have adequate trading history for our common stock, the expected volatility is estimated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. Subsequent to the IPO, we began to consider our own historic volatility. For purposes of identifying comparable companies, we selected companies with comparable characteristics to us, 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. We will continue to apply this process using the same or similar comparable entities until a sufficient amount of historical information regarding the volatility of our own stock 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* – We have never paid dividends on our common stock and have no plans to pay dividends on our common stock. Therefore, we used an expected dividend yield of zero.

Prior to our IPO in April 2016, the fair value of the shares of common stock underlying our share-based awards were estimated on each grant date by our board of directors. In order to determine the fair value of our common stock underlying option grants, our board of directors considered, among other things, timely valuations of our common stock prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants Practice Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. Given the absence of a public trading market for our capital stock, our board of directors exercised reasonable judgment and considered a number of objective and subjective factors to determine the best estimate of the fair value of our common stock, including our stage of development; progress of our research and development efforts; the rights, preferences and privileges of our convertible preferred stock relative to those of our common stock; equity market conditions affecting comparable public companies and the lack of marketability of our common stock. Following our IPO, we established a policy of using the closing sale price per share of our common stock as quoted on The Nasdaq Global Market on the date of grant for purposes of determining the exercise price per share of our share-based awards to purchase common stock.

## Results of Operations

### Comparison of the Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Dollar Change	% Change
	2018	2017		
	(dollars in thousands)			
Revenues:				
Grant	\$ 3,888	\$ 5,205	\$ (1,317)	-25%
Operating expenses:				
Research and development	\$ 36,719	\$ 22,815	\$ 13,904	61%
General and administrative	12,632	10,066	2,566	25%
Total operating expenses	49,351	32,881	16,470	50%
Loss from operations	(45,463)	(27,676)	(17,787)	64%
Interest income	1,172	482	690	143%
Other expense	(57)	(42)	(15)	36%
Net loss	\$ (44,348)	\$ (27,236)	\$ (17,112)	63%

**Grant Revenues.** Grant revenues decreased by \$1.3 million, or 25%, to \$3.9 million for the year ended December 31, 2018 from \$5.2 million for the year ended December 31, 2017. The decrease was due to the grant contract ending 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 \$13.9 million, or 61%, to \$36.7 million for the year ended December 31, 2018 from \$22.8 million for the year ended December 31, 2017. The change in research and development expenses was primarily due to:

- Higher personnel-related expenses, which increased by \$2.8 million as a result of additional employee headcount to expand our clinical development capabilities and internal research laboratory team;
- Higher clinical development expenses, which increased by \$9.5 million as a result of advancing and exceeding enrollment of our Phase 1/2 clinical trial for pegzilarginase in patients with Arginase 1 Deficiency, initiating and completing enrollment of three single agent cohort expansions for the Phase 1 trial in patients with advanced solid tumors, and advancing and completing enrollment of our Phase 1 combination trial in patients with small cell lung cancer;
- Higher nonclinical expenses, which increased by \$0.4 million as a result of advancing our toxicology studies to support continued clinical development of pegzilarginase; and
- Higher manufacturing expenses, which increased by \$1.0 million primarily as a result of a ramp-up in manufacturing activities for pegzilarginase.

**General and Administrative Expenses.** General and administrative expenses increased by \$2.6 million, or 25%, to \$12.6 million for the year ended December 31, 2018 from \$10.1 million for the year ended December 31, 2017. The increase in general and administrative expenses was primarily due to additional employee headcount and compensation to support company growth. Non-cash stock compensation expense accounted for \$1.1 million of the increase.

**Interest Income.** The increase in interest income to \$1.2 million for the year ended December 31, 2018 from \$0.5 million for the year ended December 31, 2017 was primarily due to increasing yield rates, purchasing investments with greater maturity terms, and the investment of additional funds received as a result of our public offerings in April 2018 and October 2018.

### Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016, together with the changes in those items in dollars and as a percentage:

	Year Ended December 31,		Dollar Change	% Change
	2017	2016		
	(dollars in thousands)			
Revenues:				
Grant	\$ 5,205	\$ 4,628	\$ 577	12%
Operating expenses:				
Research and development	\$ 22,815	\$ 18,143	\$ 4,672	26%
General and administrative	10,066	8,391	1,675	20%
Total operating expenses	32,881	26,534	6,347	24%
Loss from operations	(27,676)	(21,906)	(5,770)	26%
Interest income	482	244	238	98%
Other expense	(42)	(36)	(6)	17%
Net loss	\$ (27,236)	\$ (21,698)	\$ (5,538)	26%

**Grant Revenues.** Grant revenues increased by \$0.6 million, or 12%, to \$5.2 million for the year ended December 31, 2017 from \$4.6 million for the year ended December 31, 2016. The increase was primarily due to additional research and development costs associated with the clinical trials for pegzilarginase in cancer patients, for which we recognized grant revenue pursuant to the Grant Contract.

*Research and Development Expenses.* Research and development expenses increased by \$4.7 million, or 26%, to \$22.8 million for the year ended December 31, 2017 from \$18.1 million for the year ended December 31, 2016. The change in research and development expenses was due to:

- Higher personnel-related expenses, which increased by \$3.2 million as a result of additional employee headcount to strengthen our management team and expand our internal regulatory, research laboratory, and clinical development capabilities;
- Higher manufacturing expenses, which increased by \$2.2 million as a result of process scale-up for pegzilarginase and additional manufacturing activities for pipeline development;
- Higher clinical development expenses, which increased by \$1.6 million as a result of advancing our Phase 1/2 clinical trial for pegzilarginase in patients with Arginase 1 Deficiency, completing our Phase 1 dose escalation trial in patients with advanced solid tumors, preparing for three solid tumor single agent cohort expansions, and preparing for our Phase 1/2 combination trial in patients with small cell lung cancer; and
- Lower nonclinical expenses, which decreased by \$2.3 million as a result of completing toxicology studies in 2016, which supported the multi-dose clinical trials related to pegzilarginase for patients with Arginase 1 Deficiency.

*General and Administrative Expenses.* General and administrative expenses increased by \$1.7 million, or 20%, to \$10.1 million for the year ended December 31, 2017 from \$8.4 million for the year ended December 31, 2016. The increase in general and administrative expenses was primarily due to an increase in employee compensation, consulting, and facility costs.

*Interest Income.* Interest income consists of interest earned on our cash, cash equivalents, and marketable securities. The increase in interest income to \$0.5 million for the year ended December 31, 2017 from \$0.2 million for the year ended December 31, 2016 was primarily due to increasing yield rates and purchasing investments with greater terms.

## **Liquidity and Capital Resources**

### **Sources of liquidity**

We are a 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, 2018, we have funded our operations primarily by raising an aggregate of \$182.5 million of gross proceeds from the sale and issuance of convertible preferred and common equity securities and collecting \$19.8 million in 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 approximately \$69.0 million, resulting in net proceeds of \$64.5 million after deducting underwriting discounts and commissions and estimated offering costs. Additionally, a new shelf registration statement on Form S-3 was declared effective in February 2019 by the SEC for the offering, issuance and sale by us of up to \$200.0 million (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 with Jefferies LLC, as sales agent and underwriter, to issue and sell shares of our common stock for an aggregate offering price of \$60.0 million under an at-the-market (2018 ATM) offering program. After the 2019 Registration Statement was declared effective by the SEC in February 2019, \$60.0 million of our common stock remain available for sale pursuant to the 2018 ATM program.

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 April 2016, we completed our IPO and sold 5,481,940 shares of common stock for aggregate proceeds of \$47.3 million, net of 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 lead product candidate, pegzilarginase. 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 our clinical trials in 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 oncology indications, and to expand development for AEB4104 in patients with Homocystinuria and AEB5100 in patients with Cystinuria. As such, we plan to increase our research and development expenditures for the foreseeable future with nonclinical studies, clinical trials, manufacturing and an integrated biomarker strategy. We expect our principal expenditures during this time period to include expenses for the following:

- funding the continuing development of pegzilarginase;
- 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 \$116.9 million as of December 31, 2018. We anticipate that we will continue to generate losses into the foreseeable future 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 available cash, cash equivalents, and marketable securities of \$74.5 million as of December 31, 2018, in conjunction with the net proceeds received from our public offering in February 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

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

	Year Ended December 31,		
	2018	2017	2016
Net cash and cash equivalents (used in) provided by:			
Operating activities	\$ (32,193)	\$ (24,615)	\$ (18,840)
Investing activities	(15,231)	(22,529)	(12,076)
Financing activities	57,068	12,213	49,370
Net increase (decrease) in cash and cash equivalents	<u>\$ 9,644</u>	<u>\$ (34,931)</u>	<u>\$ 18,454</u>

### Cash used in operating activities

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 operating activities for the year ended December 31, 2017 was \$24.6 million and reflected a net loss of \$27.2 million. The cash impact of our net loss was offset by non-cash expenses of \$2.5 million for stock-based compensation and \$0.3 million for depreciation and amortization. The change in operating assets and liabilities of \$0.2 million was primarily due to an increase in accrued and other liabilities driven by additional research and development activities, offset by an increase in grant accounts receivable due to the timing of payments and additional qualifying costs paid prior to reimbursement.

Cash used in operating activities for the year ended December 31, 2016 was \$18.8 million and reflected a net loss of \$21.7 million. The cash impact of our net loss was offset in part by non-cash expenses of \$1.2 million for stock-based compensation and \$0.2 million for depreciation and amortization. The change in operating assets and liabilities of \$1.5 million was primarily due to an increase in accrued and other liabilities driven by accrued research and development costs.

### Cash used in investing activities

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 used in investing activities for the year ended December 31, 2017 was \$22.5 million and consisted of \$64.1 million in purchases of marketable securities and \$0.6 million in purchases of property and equipment primarily to develop an internal research laboratory, offset by \$42.2 million in maturities of marketable securities.

Cash used in investing activities for the year ended December 31, 2016 was \$12.1 million and primarily consisted of \$20.4 million in purchases of marketable securities and \$0.2 million in purchases of property and equipment offset by \$8.4 million in maturities of marketable securities.

### Cash provided by financing activities

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.

Cash provided by financing activities for the year ended December 31, 2017 was \$12.2 million, which consisted of \$12.3 million from a follow-on public offering of our common stock, offset by \$0.6 million in underwriting discounts and commissions and \$0.3 million in offering costs, and \$0.8 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, 2016 was \$49.4 million, which consisted of \$54.8 million from the IPO in April 2016, offset by \$3.8 million in underwriting discounts and commissions and \$1.7 million in offering costs, and \$0.1 million in sale of common stock under our 2016 Employee Stock Purchase Plan.

### Contractual Obligations

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

	Payments Due by Period			
	Less than 1 year	1 to 3 years	4 to 5 years	More than 5 years
Operating leases	\$ 397	\$ 492	\$ —	\$ —

In September 2016, we amended our operating lease agreement for office space in Austin, Texas. The amended lease increased the office space and extended the lease term through December 31, 2020. The total estimated rent payments over the remaining term of the lease as of December 31, 2018 is approximately \$0.6 million.

In October 2018, we amended and extended our separate lease agreement for laboratory space in Austin, Texas, which will expire in September 2021. The total estimated rent payments over the remaining term of the lease as of December 31, 2018 is approximately \$0.3 million.

### 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, 2018, 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. The new standard is effective for fiscal years and interim periods beginning after December 15, 2018, with early adoption permitted.

In July 2018, the FASB issued ASU No. 2018-11, Leases (Topic 842): Targeted Improvements, which provides entities with an additional transition method. Under ASU 2018-11, entities have the option of initially applying Topic 842 at the adoption date, rather than at the beginning of the earliest comparative period presented, and recognizing the cumulative effect of applying the new standard as an adjustment to beginning retained earnings in the year of adoption while continuing to present all prior periods under previous lease accounting guidance. We elected this transition method with an adoption date of January 1, 2019. The new standard provides a number of optional practical expedients in transition. We plan to elect all of the available practical expedients.

We expect the most significant effects of adopting this standard will primarily relate to (a) the recognition of ROU assets and lease liabilities on the balance sheet in relation to its existing operating lease agreements for the office and laboratory spaces in Austin, Texas; and (b) providing significant new disclosures about leasing activities. The adoption of this standard is not expected 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 are currently evaluating the impact that the adoption of ASU 2018-15 will have 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, 2018, we held \$74.5 million in cash, cash equivalents, and marketable securities, all of which was denominated in U.S. dollar assets, and consisting primarily of investments in reverse repurchase agreements, commercial paper, and U.S. government securities.

**AEGLEA BIOTHERAPEUTICS, INC.**  
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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, 2018 and 2017, and the related consolidated statements of operations, comprehensive loss, changes in convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018 in conformity with 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 audit 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  
March 7, 2019

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,	
	2018	2017
<b>ASSETS</b>		
<b>CURRENT ASSETS</b>		
Cash and cash equivalents	\$ 22,461	\$ 12,817
Marketable securities	52,052	37,482
Accounts receivable - grant	—	3,078
Prepaid expenses and other current assets	2,158	1,614
Total current assets	76,671	54,991
Property and equipment, net	1,018	854
Other non-current assets	50	232
<b>TOTAL ASSETS</b>	<b>\$ 77,739</b>	<b>\$ 56,077</b>
<b>LIABILITIES AND STOCKHOLDERS' EQUITY</b>		
<b>CURRENT LIABILITIES</b>		
Accounts payable	\$ 663	\$ 389
Deferred revenue	—	20
Accrued and other current liabilities	9,576	5,220
Total current liabilities	10,239	5,629
Other non-current liabilities	72	111
<b>TOTAL LIABILITIES</b>	<b>10,311</b>	<b>5,740</b>
Commitments and Contingencies (Note 13 and 15)		
<b>STOCKHOLDERS' EQUITY</b>		
Preferred stock, \$0.0001 par value; 10,000,000 shares authorized as of December 31, 2018 and 2017; no shares issued and outstanding as of December 31, 2018 and 2017	—	—
Common stock, \$0.0001 par value; 500,000,000 shares authorized as of December 31, 2018 and 2017, 24,140,097 shares and 16,670,188 shares issued and outstanding as of December 31, 2018 and 2017, respectively	2	2
Additional paid-in capital	184,314	122,950
Accumulated other comprehensive loss	(27)	(102)
Accumulated deficit	(116,861)	(72,513)
<b>TOTAL STOCKHOLDERS' EQUITY</b>	<b>67,428</b>	<b>50,337</b>
<b>TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY</b>	<b>\$ 77,739</b>	<b>\$ 56,077</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,		
	2018	2017	2016
<b>Revenues:</b>			
Grant	\$ 3,888	\$ 5,205	\$ 4,628
<b>Operating expenses:</b>			
Research and development	36,719	22,815	18,143
General and administrative	12,632	10,066	8,391
Total operating expenses	49,351	32,881	26,534
Loss from operations	(45,463)	(27,676)	(21,906)
<b>Other income (expense):</b>			
Interest income	1,172	482	244
Other expense	(57)	(42)	(36)
Total other income	1,115	440	208
Net loss	\$ (44,348)	\$ (27,236)	\$ (21,698)
Net loss per share, basic and diluted	\$ (2.13)	\$ (1.80)	\$ (2.22)
Weighted-average common shares outstanding, basic and diluted	20,822,560	15,128,192	9,791,728

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,		
	2018	2017	2016
Net loss	\$ (44,348)	\$ (27,236)	\$ (21,698)
Other comprehensive income (loss):			
Unrealized gain (loss) on marketable securities	75	(98)	(3)
Total comprehensive loss	\$ (44,273)	\$ (27,334)	\$ (21,701)

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

**Aeglea BioTherapeutics, Inc.**  
**Consolidated Statements of Changes in Convertible Preferred Stock and Stockholders' Equity (Deficit)**

(In thousands)

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount				
<b>Balances—December 31, 2015</b>	2,173	\$ 13,573	5,000	\$ 44,738	757	\$ —	\$ 1,373	\$ (23,579)	\$ (1)	\$ (22,207)
Conversion of preferred stock to common stock upon initial public offering	(2,173)	(13,573)	(5,000)	(44,738)	7,173	1	58,310	—	—	58,311
Issuance of common stock in connection with initial public offering, net of offering costs	—	—	—	—	5,482	—	47,266	—	—	47,266
Issuance of common stock in connection with employee stock purchase plan	—	—	—	—	19	—	76	—	—	76
Stock-based compensation expense	—	—	—	—	—	—	1,221	—	—	1,221
Unrealized loss on marketable securities	—	—	—	—	—	—	—	—	(3)	(3)
Net loss	—	—	—	—	—	—	—	(21,698)	—	(21,698)
<b>Balances—December 31, 2016</b>	—	\$ —	—	\$ —	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)
<b>Balances—December 31, 2017</b>	—	\$ —	—	\$ —	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)
<b>Balances—December 31, 2018</b>	—	\$ —	—	\$ —	24,140	\$ 2	\$ 184,314	\$ (116,861)	\$ (27)	\$ 67,428

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,		
	2018	2017	2016
<b>CASH FLOWS FROM OPERATING ACTIVITIES</b>			
Net loss	\$ (44,348)	\$ (27,236)	\$ (21,698)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	293	249	132
Purchase net discount (premium) on marketable securities	907	9	(146)
Net (accretion of discount) amortization of premium on marketable securities	(593)	75	101
Stock-based compensation	4,280	2,492	1,221
Research and development services settled with stock	107	15	110
Other, net	(40)	(21)	(10)
Changes in operating assets and liabilities:			
Accounts receivable - grant	3,078	(1,863)	482
Prepaid expenses and other assets	(261)	(114)	(924)
Accounts payable	239	164	(8)
Deferred revenue	(20)	(51)	71
Accrued and other liabilities	4,165	1,666	1,829
Net cash used in operating activities	<u>(32,193)</u>	<u>(24,615)</u>	<u>(18,840)</u>
<b>CASH FLOWS FROM INVESTING ACTIVITIES</b>			
Purchases of property and equipment	(422)	(619)	(212)
Purchases of marketable securities	(62,179)	(64,115)	(20,390)
Proceeds from maturities of marketable securities	47,370	42,205	8,446
Decrease in restricted cash	—	—	80
Net cash used in investing activities	<u>(15,231)</u>	<u>(22,529)</u>	<u>(12,076)</u>
<b>CASH FLOWS FROM FINANCING ACTIVITIES</b>			
Proceeds from issuance of common stock in public and at-the-market offerings, net of offering costs	54,048	11,380	49,294
Proceeds from employee stock plan purchases and stock option exercises	3,020	833	76
Net cash provided by financing activities	<u>57,068</u>	<u>12,213</u>	<u>49,370</u>
<b>NET INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS</b>	<u>9,644</u>	<u>(34,931)</u>	<u>18,454</u>
<b>CASH AND CASH EQUIVALENTS</b>			
Beginning of period	12,817	47,748	29,294
End of period	<u>\$ 22,461</u>	<u>\$ 12,817</u>	<u>\$ 47,748</u>
<b>Supplemental Disclosure of Non-Cash Investing and Financing Information:</b>			
Unpaid amounts related to purchase of property and equipment	\$ 92	\$ 57	\$ 172
Conversion of Series A convertible preferred stock to common stock upon initial public offering	\$ —	\$ —	\$ 13,573
Conversion of Series B convertible preferred stock to common stock upon initial public offering	\$ —	\$ —	\$ 44,738

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

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

Aeglea BioTherapeutics, Inc. ("Aeglea" or the "Company") is a biotechnology company that designs and develops innovative human enzyme therapeutics for patients with rare genetic diseases and cancer. 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 (the "LLC Conversion") on March 10, 2015. The Company operates in one segment and has its principal offices in Austin, Texas.

### **Liquidity**

As of December 31, 2018, the Company had working capital of \$66.4 million, an accumulated deficit of \$116.9 million, and cash, cash equivalents, and marketable securities of \$74.5 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 and development 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, in conjunction with the net proceeds received from a public offering in February 2019 (see Note 16). 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, fair values of preferred and common stock, 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.

Prior to becoming a public company, the Company utilized significant estimates and assumptions in determining the fair value of its common stock. The board of directors determined the estimated fair value of common stock based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector, the price at which the Company sold shares of convertible preferred stock, the superior rights and preferences of securities senior to the Company's common stock, and the marketability at the time. The Company utilized valuation methodologies in accordance with the American Institute of Certified Public Accountants Practice Guide, *Audit and Accounting Practice Aid Series: Valuation of Privately-Held-Company Securities Issued as Compensation*, to estimate the fair value of common stock (see Notes 3, 7, and 9).

### **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. There were no realized gains or losses on marketable securities for the years ended December 31, 2018, 2017, and 2016. Interest on marketable securities is included in interest income.

### **Concentration of Credit Risk**

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents, and marketable securities. The Company's investment policy limits investments to high credit quality securities issued by the U.S. government, U.S. government-sponsored agencies and highly rated banks, subject to certain concentration limits and restrictions on maturities. The Company's cash, cash equivalents, and marketable securities 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 and cash equivalents 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 and cash equivalents 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, 2018, 2017, and 2016.

### **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. The Company has not experienced any material deviations between accrued and actual research and development expenses.

### **Leases**

The Company entered into lease agreements for its office and laboratory facilities. The leases are classified as operating leases. The Company records rent expense on a straight-line basis over the term of the leases and, accordingly records the difference between cash rent payments and the recognition of rent expense as a deferred rent liability. Incentives granted under the Company's facilities leases, including allowances to fund leasehold improvements, are deferred and are recognized as adjustments to rental expense on a straight-line basis over the term of the lease.

### **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, and marketable securities. 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 8).

### **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.

Certain research and development costs incurred were settled contractually by the Company issuing a variable number of the Company's shares determined by dividing the fixed monetary amount of costs incurred by the issuance-date fair value of the issuable shares. The Company recorded research and development expense for these costs and accrued for the fixed monetary amount as an accrued liability as the services were rendered until the amount was settled. The remaining Company obligation to settle these costs with Company shares was converted to a cash-based payment through a contract amendment with the service provider.

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 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. The Company elected to early adopt ASU 2018-07, *Compensation – Stock Compensation (Topic 718)* effective January 1, 2018. All non-employee share-based payment awards granted prior to adoption were remeasured at fair value as of the adoption date. There was no material impact on the Company's consolidated financial statements from the adoption. All non-employee share-based payment awards granted after adoption are measured at grant-date fair value. 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 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. The new standard is effective for fiscal years and interim periods beginning after December 15, 2018, with early adoption permitted.

In July 2018, the FASB issued ASU No. 2018-11, Leases (Topic 842): Targeted Improvements, which provides entities with an additional transition method. Under ASU 2018-11, entities have the option of initially applying Topic 842 at the adoption date, rather than at the beginning of the earliest comparative period presented, and recognizing the cumulative effect of applying the new standard as an adjustment to beginning retained earnings in the year of adoption while continuing to present all prior periods under previous lease accounting guidance. The Company elected this transition method with an adoption date of January 1, 2019. The new standard provides a number of optional practical expedients in transition. The Company plans to elect all of the available practical expedients.

The Company expects that the most significant effects of adopting this standard will primarily relate to (a) the recognition of ROU assets and lease liabilities on the balance sheet in relation to its existing operating lease agreements for the office and laboratory spaces in Austin, Texas; and (b) providing significant new disclosures about leasing activities. The adoption of this standard is not expected to have a material impact on the Company's 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 is currently evaluating the impact that the adoption of ASU 2018-15 will have 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, 2018			Total
	Level 1	Level 2	Level 3	
<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
Total financial assets	<u>\$ 7,180</u>	<u>\$ 64,278</u>	<u>\$ —</u>	<u>\$ 71,458</u>

	December 31, 2017			
	Level 1	Level 2	Level 3	Total
<b>Financial Assets</b>				
Money market funds	\$ 1,674	\$ —	\$ —	\$ 1,674
Reverse repurchase agreements	—	7,250	—	7,250
U.S. treasury securities	1,501	—	—	1,501
U.S. government securities	—	35,981	—	35,981
<b>Total financial assets</b>	<b>\$ 3,175</b>	<b>\$ 43,231</b>	<b>\$ —</b>	<b>\$ 46,406</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, commercial paper, and U.S. government securities 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.

#### Valuation Approach for the Company's Shares and Related Instruments

Prior to the IPO, the Company valued its common stock and common shares by taking into consideration, among other things, its most recent valuation of common stock and common shares prepared by an unrelated third-party valuation firm in accordance with the guidance provided by the American Institute of Certified Public Accountants Practice Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. Given the absence of a public trading market for the Company's capital stock, the Company exercised reasonable judgment and considered a number of objective and subjective factors, including changes since the date of the most recent contemporaneous valuation through the date of grant. The Company estimated the fair value of each class of common shares, preferred shares, and common stock by utilizing either a hybrid of the Probability-Weighted Expected Return Method ("PWERM") and the Option Pricing Method ("OPM") or the OPM, both valuation methodologies are based on the Backsolve Method, a form of the market approach. The hybrid valuation methodology applied the PWERM utilizing the probability of going public scenarios and a liquidation scenario. The OPM valuation methodology included estimates and assumptions that require the Company's judgment. Inputs used to determine estimated fair value of the shares include the equity value of the Company, probabilities of going public by term (from 12.5% to 80% with terms from 0.55 to 0.13 years), risk-adjusted discount rate (30%), discount for lack of marketability (from 30% to 7.5%), expected timing of the liquidity event (from 2.8 to 3.0 years), a risk-free interest rate (from 0.8% to 1.1%) and the expected volatility (70%). Generally, increases or decreases in these unobservable inputs would result in a directionally similar impact to the fair value measurement of the Company's shares. Following the IPO, the Company utilizes the closing sale price per share of its common stock as quoted on The Nasdaq Global Market on the date of grant for purposes of determining the fair value of its common stock.

#### 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, 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>

	December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
<b>Cash equivalents:</b>				
Money market funds	\$ 1,674	\$ —	\$ —	\$ 1,674
Reverse repurchase agreements	7,250	—	—	7,250
<b>Total cash equivalents</b>	<b>8,924</b>	<b>—</b>	<b>—</b>	<b>8,924</b>
<b>Marketable securities:</b>				
U.S. treasury securities	1,502	—	(1)	1,501
U.S. government securities	36,082	—	(101)	35,981
<b>Total marketable securities</b>	<b>\$ 37,584</b>	<b>\$ —</b>	<b>\$ (102)</b>	<b>\$ 37,482</b>

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

As of December 31, 2018 and 2017, 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, 2018 and 2017 were \$45.6 million and \$37.5 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, 2018 and 2017.

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

	December 31,	
	2018	2017
Due in one year or less	\$ 52,052	\$ 34,498
Due in 1 - 2 years	—	2,984
<b>Total marketable securities</b>	<b>\$ 52,052</b>	<b>\$ 37,482</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,	
	2018	2017
Laboratory equipment	\$ 981	\$ 651
Furniture and office equipment	227	209
Computer equipment	89	111
Software	99	99
Leasehold improvements	374	271
Property and equipment, gross	1,770	1,341
Less: Accumulated depreciation and amortization	(752)	(487)
<b>Property and equipment, net</b>	<b>\$ 1,018</b>	<b>\$ 854</b>

Depreciation and amortization expense for the years ended December 31, 2018, 2017, and 2016 was \$0.3 million, \$0.2 million, and \$0.1 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,	
	2018	2017
Accrued compensation	\$ 2,643	\$ 1,837
Accrued contracted research and development costs	5,993	2,552
Accrued professional and consulting fees	807	672
Accrued and other current liabilities	133	159
Total accrued and other current liabilities	<u>\$ 9,576</u>	<u>\$ 5,220</u>

## 7. Convertible Preferred Stock and Stockholders' Equity

As of December 31, 2015, the Company had 2,172,520 shares of Series A convertible preferred stock outstanding and 4,999,976 shares of Series B convertible preferred stock outstanding with a related carrying value of \$13.6 million and \$44.7 million, respectively. Immediately prior to the closing of the Company's initial public offering ("IPO") in April 2016, all of the outstanding convertible preferred stock was automatically converted into 7,172,496 shares of common stock on a one-to-one basis, with the aggregate total carrying value of \$58.3 million reclassified to common stock and additional paid-in capital. As of December 31, 2018 and 2017, there were no shares of preferred stock outstanding.

On April 12, 2016, the Company closed an IPO of its common stock, which resulted in the sale of 5,481,940 shares of its common stock at a public offering price of \$10.00 per share, including 481,940 shares of common stock issued upon the partial exercise by the underwriters of their option to purchase additional shares. The Company received \$47.3 million in aggregate cash proceeds, net of underwriting discounts and commissions of \$3.8 million and offering costs of \$3.7 million incurred by the Company.

In connection with the IPO, the Company amended its Restated Certificate of Incorporation to change the authorized capital stock to 510,000,000 shares 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, 2018, no common stock dividends have been declared by the board of directors.

### *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.

### *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.

## **8. 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 years ended December 31, 2018, 2017, and 2016 the Company recognized \$3.9 million, \$5.2 million, and \$4.6 million, respectively, in grant revenues for qualified expenditures under the grant. As of December 31, 2018, all grant proceeds had been collected. As of December 31, 2017, the Company had an outstanding grant receivable of \$3.1 million for the grant expenditures that were paid but had not been reimbursed and deferred revenue of \$20,000 for proceeds received but for which the costs had not been incurred or the conditions of the award had not been met.

## **9. 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, 2018, a total of 268,716 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, 2018, the total number of shares reserved for issuance under the 2016 Plan was 4,750,902, of which 2,760,071 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, 2018, the total number of shares reserved for issuance under the 2018 Plan was 1,100,000, of which 113,900 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.

As of December 31, 2018, the reserve remaining and available for future issuance under the 2016 ESPP was 50,851 shares.

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.

The following table summarizes employee and non-employee stock option activity for the year ended December 31, 2018:

	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, 2017</b>	2,361,360	\$ 5.21	8.72	\$ 2,482
Granted	1,668,800	8.03		
Exercised	(521,665)	5.42		
Forfeited	(365,808)	5.20		
<b>Outstanding as of December 31, 2018</b>	<u>3,142,687</u>	\$ 6.67	8.52	\$ 4,798
<b>Options vested and expected to vest as of December 31, 2018</b>	<u>2,939,785</u>	\$ 6.49	8.45	\$ 4,786
<b>Options exercisable as of December 31, 2018</b>	<u>1,160,819</u>	\$ 5.85	7.68	\$ 2,470

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, 2018, 2017, and 2016, the weighted-average grant date fair value of options granted was \$8.03, \$5.22, and \$7.04, respectively. The total intrinsic value of options exercised during the years ended December 31, 2018 and 2017 was \$1.9 million and \$0.3 million, respectively. There were no option exercises during the year ended December 31, 2016.

There were no stock options issued to non-employees during the years ended December 31, 2018, 2017, and 2016. For the year ended December 31, 2018, 6,626 non-employee stock options vested in the period. For the years ended December 31, 2017 and 2016, no non-employee stock options vested in the period.

### Restricted Common Stock

The Company issued 253,232 restricted stock awards ("RSAs") during the year ended December 31, 2015 with time-based and performance-based vesting conditions. Unvested shares of restricted common stock may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award.

The following table summarizes employee and non-employee restricted stock activity for the year ended December 31, 2018:

	Shares	Weighted Average Grant Date Fair Value
<b>Unvested restricted common stock as of December 31, 2017</b>	33,307	\$ 1.84
Granted	—	—
Vested	(26,444)	1.87
Forfeited	—	—
<b>Unvested restricted common stock as of December 31, 2018</b>	<u>6,863</u>	<u>\$ 1.73</u>

The fair value of RSAs that vested during the years ended December 31, 2018, 2017, and 2016 was \$0.2 million, \$0.2 million, and \$0.3 million, respectively. There were no RSAs granted to non-employees during the years ended December 31, 2018, 2017, and 2016. For the year ended December 31, 2018, 21,645 non-employee RSAs vested in the period. For the years ended December 31, 2017 and 2016, no non-employee RSAs 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, 2018, 2017, and 2016 was as follows (in thousands):

	Year Ended December 31,					
	2018		2017		2016	
	Employees	Non-Employees	Employees	Non-Employees	Employees	Non-Employees
Research and development	\$ 1,440	\$ 234	\$ 961	\$ —	\$ 389	\$ —
General and administrative	2,606	—	1,531	—	832	—
<b>Total stock-based compensation expense</b>	<u>\$ 4,046</u>	<u>\$ 234</u>	<u>\$ 2,492</u>	<u>\$ —</u>	<u>\$ 1,221</u>	<u>\$ —</u>

No related tax benefits were recognized for the years ended December 31, 2018, 2017, and 2016 (see Note 11).

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, 2018, 2017, and 2016. 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, the Company's board of directors approved the acceleration of vesting and an extension in the exercise period for all outstanding equity awards held by one director upon his resignation (see Note 14). 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, 2018, the Company had an aggregate of \$8.6 million of unrecognized stock-based compensation expense for options outstanding, which is expected to be recognized over a weighted average period of 2.7 years. There was no unrecognized stock-based compensation expense for RSAs outstanding as of December 31, 2018.

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 IPO, the Company 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,		
	2018	2017	2016
<b>2018 Plan, 2016 Plan, and 2015 Plan</b>			
Expected term (in years)	5.20	5.88	5.99
Expected volatility	74%	86%	87%
Risk-free interest	2.42%	2.00%	1.28%
Dividend yield	0%	0%	0%
<b>2016 ESPP</b>			
Expected term (in years)	0.50	0.50	0.45
Expected volatility	66%	78%	82%
Risk-free interest	2.20%	1.06%	0.50%
Dividend yield	0%	0%	0%

## 10. 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, 2018, 2017, 2016, the Company provided \$0.2 million, \$0.1 million, and \$0.1 million, respectively, in contributions to the plan.

## 11. Income Taxes

For the years ended December 31, 2018, 2017, and 2016, 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,		
	2018	2017	2016
Tax provision derived by applying the federal statutory rate to income before income taxes	\$ (9,313)	\$ (9,260)	\$ (7,377)
Permanent differences and other	264	296	333
Federal tax credits	(1,211)	(1,294)	(1,921)
State tax credits	464	(284)	(404)
Change in tax rate	—	7,869	—
Change in the valuation allowance	9,796	2,673	9,369
Income tax expense /(benefit)	\$ —	\$ —	\$ —

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

	December 31,	
	2018	2017
<b>Deferred tax assets</b>		
Net operating loss carryforward	\$ 20,276	\$ 12,170
Intangible assets	38	29
Accrued expense	508	333
Stock-based compensation	682	386
Federal tax credits	7,260	5,572
State tax credits	359	824
Other	73	75
<b>Total deferred tax assets</b>	<b>29,196</b>	<b>19,389</b>
<b>Deferred tax liabilities</b>		
Depreciable assets	\$ (74)	\$ (63)
<b>Total deferred tax liabilities</b>	<b>(74)</b>	<b>(63)</b>
<b>Less: Valuation allowance</b>	<b>(29,122)</b>	<b>(19,326)</b>
<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 changes 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 income tax effects from the 2017 Tax Act for the year ended December 31, 2018.

The Company has established a 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 \$9.8 million, \$2.7 million, and \$9.4 million during the years ended December 31, 2018, 2017, and 2016, respectively, primarily due to continuing loss from operations.

As of December 31, 2018 and 2017, the Company had U.S. net operating loss carryforwards ("NOL") of \$96.6 million and \$58.0 million, respectively. As of December 31, 2018 and 2017, the Company had U.S. tax credit carryforwards of \$7.3 million and \$5.6 million, respectively, and state tax credit carryforwards of \$0.4 million and \$1.0 million, respectively. The net operating loss and tax credit carryforwards 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.

As part of the PATH Act of 2015, certain eligible companies have the ability to convert a portion of their research tax credits to offset payroll tax liabilities. During the year ended December 31, 2017, the Company converted \$0.5 million of its research tax credit to offset payroll tax liabilities. The Company did not convert any research tax credits to offset payroll tax liabilities during the years ended December 31, 2018 and 2016. As of December 31, 2018 and 2017, the Company held a payroll tax credit receivable of \$0.3 million and \$0.4 million, respectively, in prepaid expenses and other current assets and \$0.0 million and \$0.1 million, respectively, in other non-current assets.

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 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, 2018 and 2017, there were no amounts recorded for uncertain tax positions.

## 12. Net Loss Per Share

The Company computed net loss attributable per common stockholder using the two-class method required for participating securities through the date of the IPO. Immediately prior to the closing of the IPO, all outstanding convertible preferred stock was converted into common stock (see Note 7). The Company considered convertible preferred stock to be participating securities. In the event that the Company had paid out distributions, holders of convertible preferred stock would have participated in the distribution.

The two-class method is an earnings (loss) allocation method under which earnings (loss) per share is calculated for common stock and participating security considering a participating security's rights to undistributed earnings (loss) as if all such earnings (loss) had been distributed during the period. The convertible preferred stock did not have an obligation to fund losses and are therefore excluded from the calculation of basic net loss per share.

Basic and diluted net loss per share is computed by dividing net loss by the weighted-average number of that class of common stock outstanding during the period. 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,		
	2018	2017	2016
Series A convertible preferred stock	—	—	611,392
Series B convertible preferred stock	—	—	1,407,097
Unvested restricted common stock	26,841	57,629	100,634
Options to purchase common stock	3,014,984	2,043,420	1,063,778

### 13. 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, 2018, 2017 and 2016, the Company paid \$50,000, \$30,000 and \$10,000, respectively, in annual license fees.

In connection with the above license agreements, the Company also entered into a Sponsored Research Agreement (the "SRA") with the University in December 2013, which was subsequently amended. Under the terms of this research agreement, the Company engaged the University to perform certain nonclinical research activities related to the systemic depletion of amino acids for cancer and rare genetic disease therapy. The SRA expired on August 31, 2018. For the years ended December 31, 2018, 2017, and 2016, the Company paid \$0.2 million, \$0.6 million, and \$0.8 million, respectively, to the University under the SRA.

### 14. Related Party Transactions

One of the founders ("Founder"), a non-employee member of the Company's board of directors, entered into a consulting agreement with the Company in 2014 under which the Founder would receive \$50,000 per year for a fixed number of hours of consulting and advisory services and receive equity incentive shares, which converted into 43,290 restricted stock awards and 13,852 stock options upon the LLC Conversion, with the vesting contingent on time and performance milestones being achieved.

Effective November 7, 2018, the Founder resigned from his position as a member of the Company's board of directors and is no longer deemed a related party. Upon resigning, the board of directors approved the immediate vesting of all unvested stock options and restricted stock. Additionally, the exercise period was extended from 90 days to 180 days. The acceleration of vesting and extension of the exercise period resulted in additional stock-based compensation expense (see Note 9).

For the year ended December 31, 2018, there were no payments made to the Founder under the consulting agreement. In each of the years ended December 31, 2017 and 2016, the Company paid \$50,000 to the Founder under the consulting agreement. As of December 31, 2018 and 2017, the Company had no outstanding liability to the related party.

### 15. Commitments and Contingencies

The Company leases office and laboratory space in Austin, Texas under operating leases that commenced in January 2015 and February 2017, respectively. The office lease was amended in September 2016 to increase office space and extend the term to December 31, 2020. In addition, the amended office lease provides for tenant improvement allowances on both the original space and expansion space totaling \$0.2 million.

The Company signed a new laboratory lease agreement in October 2017 for the original laboratory space, which commenced on January 1, 2018. The laboratory lease was subsequently amended in October 2018 to increase the space and extend the lease term to September 30, 2021.

As provided in the office and laboratory leases, monthly lease payments are subject to annual increases through the lease term. The Company recognizes rent expense on a straight-line basis over the non-cancellable term of each lease.

The Company is subject to security deposit requirements under the terms of the amended office lease and laboratory lease agreements, totaling \$48,000, until the expiration of the lease. The lessor is entitled to retain all or any part of the security deposit for payment in the event of any uncured default by the Company under the terms of the lease.

Future annual minimum lease payments due under non-cancellable operating leases at December 31 of each year are as follows (in thousands):

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

For the years ended December 31, 2018, 2017, and 2016, the Company incurred \$0.4 million, \$0.4 million, and \$0.2 million in rent expense under non-cancellable operating leases.

## 16. Subsequent Events

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 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 public offering were approximately \$64.5 million, after deducting underwriting discounts and commissions of \$4.1 million and estimated offering costs of \$0.4 million.

## 17. Selected Quarterly Financial Data (Unaudited)

Selected quarterly results from operations for the years ended December 31, 2018 and 2017 are as follows (in thousands, except per share amounts):

	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)

	2017 Quarter Ended			
	March 31,	June 30,	September 30,	December 31,
Grant revenues	\$ 982	\$ 1,479	\$ 1,261	\$ 1,483
Loss from operations	(6,331)	(6,720)	(7,998)	(6,627)
Net loss	(6,247)	(6,632)	(7,874)	(6,483)
Basic and diluted net loss per common share	\$ (0.47)	\$ (0.47)	\$ (0.48)	\$ (0.39)

## 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, 2018, 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, 2018. 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, 2018, 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, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

**ITEM 9B. OTHER INFORMATION**

None.

**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 2019 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 2019 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 2019 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 2019 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 2019 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 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*	<a href="#">Restated Certificate of Incorporation</a>	S-1/A	333-205001	9/14/2015	3.2	
3.4*	<a href="#">Restated Bylaws</a>	S-1/A	333-205001	9/14/2015	3.4	
4.1*	<a href="#">Form of Common Stock Certificate.</a>	S-1/A	333-205001	9/14/2015	4.1	
4.2*	<a href="#">Amended and Restated Investors' Rights Agreement, dated March 10, 2015, by and among the Registrant and certain of its stockholders, as amended.</a>	S-1	333-205001	6/16/2015	4.2	
4.3	<a href="#">Amendment #1, dated December 4, 2018, to Amendment and Restated Investors' Rights Agreement, as amended</a>					X
4.4	<a href="#">Form of Pre-Funded Warrants</a>	8-K	001-37722	2/7/2019	4.1	
10.1*	<a href="#">Form of Amended and Restated Indemnification Agreement.</a>	10Q	001-37722	8/9/2018	10.1	
10.2*†	<a href="#">2015 Equity Incentive Plan and forms of award agreements.</a>	S-1	333-205001	6/16/2015	10.2	
10.3†	<a href="#">2016 Equity Incentive Plan and forms of award agreements, as amended.</a>	10Q	001-37722	11/8/2018	10.2	
10.4*†	<a href="#">2016 Employee Stock Purchase Plan and forms of award agreements, as amended.</a>					X
10.5*†	<a href="#">2018 Equity Inducement Plan</a>	S-8	333-223614	3/13/2018	99.2	
10.6*†	<a href="#">Form of Stock Restriction Agreement.</a>	S-1	333-205001	6/16/2015	10.5	
10.7*†	<a href="#">Form of Severance Agreement</a>	8-K	001-37722	4/16/2018	10.1	
10.8*†	<a href="#">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.</a>	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*	<a href="#">Office Lease, dated November 24, 2014, between Barton Oaks Office Center, LLC and the Registrant.</a>	S-1	333-205001	6/16/2015	10.11
10.10*	<a href="#">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.</a>	10-Q	001-37722	11/9/2016	10.1
10.11*†	<a href="#">Consulting Agreement, dated February 18, 2014, by and between the Registrant and George Georgiou.</a>	S-1	333-205001	6/16/2015	10.12
10.12#	<a href="#">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</a>				X
10.13*†	<a href="#">Cancer Research Grant Contract, dated June 15, 2015, between AERase, Inc. and the Cancer Prevention Research Institute of Texas.</a>	S-1	333-205001	6/16/2015	10.15
10.14‡	<a href="#">Offer Letter, dated June 16, 2014, issued by the Registrant to Mr. Charles N. York II.</a>	10-K	001-37722	3/23/2017	10.19
10.15‡	<a href="#">Offer Letter, dated June 20, 2017, issued by the Registrant to Dr. James Wooldridge.</a>	10-K	001-37722	3/13/2018	10.17
10.16	<a href="#">Offer Letter, dated July 18, 2018, by and between the Registrant and Anthony G. Quinn</a>	8-K	001-37722	7/23/2018	10.1
10.17	<a href="#">Severance Agreement, dated July 18, 2018, by and between the Registrant and Anthony G. Quinn</a>	8-K	001-37722	7/23/2018	10.2
10.18#	<a href="#">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.</a>				X

Exhibit Number	Description of Document	Incorporate by Reference			Filed Herewith
		Form	File No.	Date of Filing	
21.1*	<a href="#">Subsidiaries of the Registrant.</a>	S-1	333-205001	6/16/2015	21.1
23.1	<a href="#">Consent of independent registered public accounting firm.</a>				
24.1	<a href="#">Power of Attorney. Reference is made to the signature page hereto.</a>				
31.1	<a href="#">Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.</a>				
31.2	<a href="#">Certification of the Principal Financial Officer, pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934.</a>				
32.1(1)	<a href="#">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.</a>				
32.2(1)	<a href="#">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.</a>				
101.INS	XBRL Instance Document.				
101.SCH	XBRL Taxonomy Extension Schema Document.				
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.				
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.				
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document.				
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document				

\* 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: March 7, 2019

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)	March 7, 2019
<u>/s/ Charles N. York II</u> Charles N. York II	Chief Financial Officer and Vice President (Principal Accounting Officer and Principal Financial Officer)	March 7, 2019
<u>/s/ Russell J. Cox</u> Russell J. Cox	Director	March 7, 2019
<u>/s/ Sandesh Mahatme, LLM</u> Sandesh Mahatme, LLM	Director	March 7, 2019
<u>/s/ Armen Shanafelt, Ph.D.</u> Armen Shanafelt, Ph.D.	Director	March 7, 2019
<u>/s/ Suzanne Bruhn, Ph.D.</u> Suzanne Bruhn, Ph.D.	Director	March 7, 2019
<u>/s/ Ivana Magovcevic-Liebisch, Ph.D.</u> Ivana Magovcevic-Liebisch, Ph.D.	Director	March 7, 2019
<u>/s/ Bryan Lawlis, Ph.D.</u> Bryan Lawlis, Ph.D.	Director	March 7, 2019

**AMENDMENT NO. 1 TO  
AMENDED AND RESTATED INVESTOR RIGHTS AGREEMENT**

This Amendment No. 1 to Amended and Restated Investor Rights Agreement (this "**Amendment**") is entered into as of December 4, 2018 by the undersigned parties to that certain Amended and Restated Investor Rights Agreement, dated as of March 10, 2015 (the "**Rights Agreement**"), by and among Aeglea BioTherapeutics, Inc., a Delaware corporation (the "**Company**") and the Investors. Capitalized terms used but not defined herein shall have the meanings ascribed to them in the Rights Agreement.

**RECITALS**

A. WHEREAS, the Company's Board of Directors has determined it is in the best interests of the Company and its stockholders to amend certain provisions in the Rights Agreement with respect to registration rights

B. WHEREAS, Section 6.6 of the Rights Agreement provides that any provision of the Rights Agreement may be amended with the written consent of the Company and the Investors holding at least 62% of voting power of all Registrable Securities then held by all Investors (the "**Requisite Holders**")

C. WHEREAS, the undersigned Investors, who collectively constitute the Requisite Holders, desire to amend the Rights Agreement all as set forth below.

NOW, THEREFORE, in consideration of the foregoing recitals and for other good and valuable consideration, the adequacy and sufficiency of which are hereby acknowledged, the undersigned hereby agree as follows:

1. Amendment to Section 3.14. Section 3.14 of the Rights Agreement is hereby amended and restated in its entirety to state the following:

"3.14 Termination of Rights. The rights of any particular Holder under this Section 3 hereof shall terminate as to any Holder on the earliest of (a) April 12, 2021, (b) the date on which such Holder ceases to hold Registrable Securities, and (c) such time as all of such Holder's Registrable Securities could be sold without any restriction on volume or manner of sale in any three-month period under Rule 144 or any successor rule."

2. Full Force and Effect. Except as expressly modified herein, the Rights Agreement shall remain in full force and effect.

3. Governing Law. This Amendment shall be governed by, and construed and interpreted in accordance with the laws of the State of Delaware as applied to agreements among Delaware residents made and to be performed entirely within the State Delaware.

4. Counterparts. This Amendment may be executed in counterparts, delivered by facsimile or portable document format (.pdf or similar format), each of which will constitute an original and all of which together will constitute one agreement.

The parties are signing this Amendment as of the date stated in the introductory clause.

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**COMPANY:**

**AEGLEA BIOTHERAPEUTICS, INC.**

By: /s/ Charles N. York II  
Charles N. York II  
Chief Financial Officer

Address: 901 S. MoPac Expressway  
Barton Oaks Plaza One Suite 250  
Austin, TX 78746

**SIGNATURE PAGE TO IRA AMENDMENT**

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The parties are signing this Amendment as of the date stated in the introductory clause.

**LILLY VENTURES FUND I LLC**

By: /s/ S. Edward Torres

Name: S. Edward Torres

Title: Managing Director

Date: December 4, 2018

**SIGNATURE PAGE TO IRA AMENDMENT**

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The parties are signing this Amendment as of the date stated in the introductory clause.

**INVESTOR:**

**NOVARTIS BIOVENTURES LTD.**

By: /s/ Bart Dzikowski

Name: Bart Dzikowski

Title: Secretary of the Board

Date: March 21, 2018

By: /s/ Florian Muellershausen

Name: Florian Muellershausen

Title: Authorized Signatory

Date: March 21, 2018

**SIGNATURE PAGE TO IRA AMENDMENT**

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The parties are signing this Amendment as of the date stated in the introductory clause.

**INVESTOR:**

**JENNISON GLOBAL HEALTHCARE MASTER FUND, LTD.**

By: Jennison Associates LLC, its Investment Manager

By: /s/ David Chan

Name: David Chan

Title: Managing Director

Date: March 22, 2018

**SIGNATURE PAGE TO IRA AMENDMENT**

## AEGLEA BIOTHERAPEUTICS, INC.

## 2016 EMPLOYEE STOCK PURCHASE PLAN

**1. PURPOSE.** Aeglea BioTherapeutics, Inc. has adopted this Plan effective as of the date of the IPO. The purpose of this Plan is to provide eligible employees of the Company and the Participating Corporations with a means of acquiring an equity interest in the Company and to enhance such employees' sense of participation in the Company's affairs. Capitalized terms not defined elsewhere in the text are defined in Section 28.

**2. ESTABLISHMENT OF PLAN.** The Company proposes to grant rights to purchase shares of Common Stock to eligible employees of the Company and its Participating Corporations pursuant to this Plan. The Company intends this Plan to qualify as an "employee stock purchase plan" under Section 423 of the Code (including any amendments to or replacements of such Section), and this Plan shall be so construed, although the Company makes no undertaking or representation to maintain such qualification. Any term not expressly defined in this Plan but defined in Section 423 of the Code shall have the definition provided by Section 423 of the Code. In addition, with regard to offers of options to purchase shares of Common Stock under the Plan to employees working for a Subsidiary or an Affiliate outside the United States, this Plan authorizes the grant of options under a Non-Section 423 Component that is not intended to meet the requirements of Section 423 of the Code provided that, to the extent necessary under Section 423 of the Code, the other terms and conditions of this Plan are met.

Subject to Section 14, a total of 165,000 shares of Common Stock is reserved for issuance under this Plan. In addition, on each January 1 for each of the calendar years beginning 2019 and ending 2026, the aggregate number of shares of Common Stock reserved for issuance under the Plan shall be increased automatically by the number of shares equal to one percent (1%) of the total number of outstanding shares of Common Stock and Common Stock equivalents outstanding on the immediately preceding December 31 (rounded down to the nearest whole share); provided, that the Board may in its sole discretion reduce the amount of the increase in any particular year. Subject to Section 14, no more than 2,900,000 shares of Common Stock may be issued over the term of this Plan. The number of shares initially reserved for issuance under this Plan and the maximum number of shares that may be issued under this Plan shall be subject to adjustments effected in accordance with Section 14. Any or all such shares may be granted under the Section 423 Component.

**3. ADMINISTRATION.** The Plan will be administered by the Committee. Subject to the provisions of this Plan and the limitations of Section 423 of the Code or any successor provision in the Code, all questions of interpretation or application of this Plan shall be determined by the Committee and its decisions shall be final and binding upon all eligible employees and Participants. The Committee will have full and exclusive discretionary authority to construe, interpret and apply the terms of this Plan, to determine eligibility, to designate the Participating Corporations, to determine whether Participating Corporations shall participate in the Section 423 Component or Non-Section 423 Component and to decide upon any and all claims filed under the Plan. Every finding, decision and determination made by the Committee will, to the full extent permitted by law, be final and binding upon all parties. Notwithstanding any provision to the contrary in this Plan, the Committee may adopt rules, sub-plans, and/or procedures relating to the operation and administration of this Plan designed to comply with local laws, regulations or customs or to achieve tax, securities law or other objectives for eligible employees outside of the United States. The Committee will have the authority to determine the Fair Market Value of the Common Stock (which determination shall be final, binding and conclusive for all purposes) in accordance with Section 8 below and to interpret Section 8 of this Plan in connection with circumstances that impact the Fair Market Value. Members of the Committee shall receive no compensation for their services in connection with the administration of this Plan, other than standard fees as established from time to time by the Board for services rendered by Board members serving on Board committees. All expenses incurred in connection

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with the administration of this Plan shall be paid by the Company. For purposes of this Plan, the Committee may designate separate offerings under the Plan (the terms of which need not be identical) in which eligible employees of one or more Participating Corporations will participate, even if the dates of the applicable Offering Periods of each such offering are identical.

#### **4. ELIGIBILITY.**

(a) Any employee of the Company or the Participating Corporations is eligible to participate in an Offering Period under this Plan, except that one or more of the following categories of employees may be excluded from eligibility under this Plan by the Committee (other than where such exclusion is prohibited by applicable law):

(i) employees who are customarily employed for twenty (20) hours or less per week;

(ii) employees who are customarily employed for five (5) months or less in a calendar year; and

(iii) employees who do not meet any other eligibility requirements that the Committee may choose to impose (within the limits permitted by the Code).

Notwithstanding the foregoing, an individual shall not be eligible if his or her participation in this Plan is prohibited by the law of any country having jurisdiction over him or her, if complying with the laws of the applicable country would cause the Plan to violate Section 423 of the Code, or if he or she is subject to a collective bargaining agreement that does not provide for participation in this Plan.

(b) No employee who, together with any other person whose stock would be attributed to such employee pursuant to Section 424(d) of the Code, owns stock or holds options to purchase stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or its Parent or Subsidiary or who, as a result of being granted an option under this Plan with respect to such Offering Period, would own stock or hold options to purchase stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or its Parent or Subsidiary shall be granted an option to purchase Common Stock under this Plan. Notwithstanding the foregoing, the rules of Section 424(d) of the Code shall apply in determining share ownership and the extent to which shares held under outstanding equity awards are to be treated as owned by the employee.

#### **5. OFFERING DATES.**

(a) Each Offering Period of this Plan may be of up to twenty-seven (27) months' duration and shall commence and end at the times designated by the Committee. Each Offering Period shall consist of one Purchase Period during which Contributions made by Participants are accumulated under this Plan.

(b) The initial Offering Period shall commence on the Effective Date and shall end with the Purchase Date that occurs on August 15, 2016 or another date selected by the Committee which is approximately six (6) months after the commencement of the initial Offering Period, but no more than twenty-seven (27) months after the commencement of the initial Offering period. The initial Offering Period shall consist of one Purchase Period. Thereafter, a six-month Offering Period shall commence on each February 16 and August 16, with each such Offering Period also consisting of one six-month Purchase Period, except as otherwise provided by an applicable sub-plan, or on such other date determined by the Committee. The Committee may at any time establish a different duration for an Offering Period or Purchase Period to be effective after the next scheduled Purchase Date, up to a maximum duration of twenty-seven (27) months.

(c) To the extent applicable, if the Fair Market Value on the first day of the current Offering Period in which a Participant is enrolled is higher than the Fair Market Value on the first day of any subsequent Purchase Period, the current Offering Period shall end, and Participant shall be automatically enrolled in the subsequent Offering Period, as specified under Section 5(a) or Section 5(b), as applicable. Any funds

accumulated in a Participant's account prior to the first day of such subsequent Offering Period will be applied to the purchase of shares on the Purchase Date immediately prior to the first day of such subsequent Offering Period, if any.

#### **6. PARTICIPATION IN THIS PLAN.**

(a) Any employee who is an eligible employee determined in accordance with Section 4 immediately prior to the initial Offering Period will be automatically enrolled in the initial Offering Period under this Plan for the maximum number of shares of Common Stock purchasable. With respect to subsequent Offering Periods, any eligible employee determined in accordance with Section 4 will be eligible to participate in this Plan, subject to the requirement of Section 6(b) hereof and the other terms and provisions of this Plan.

(b) With respect to Offering Periods after the initial Offering Period, a Participant may elect to participate in this Plan by submitting an enrollment agreement prior to the commencement of the Offering Period (or such earlier date as the Committee may determine) to which such agreement relates.

(c) Once an employee becomes a Participant in an Offering Period, then such Participant will automatically participate in each subsequent Offering Period commencing immediately following the last day of the prior Offering Period unless the Participant withdraws or is deemed to withdraw from this Plan or terminates further participation in an Offering Period as set forth in Section 11 below. A Participant who is continuing participation pursuant to the preceding sentence is not required to file any additional enrollment agreement in order to continue participation in this Plan; a Participant who is not continuing participation pursuant to the preceding sentence is required to file an enrollment agreement prior to the commencement of the Offering Period (or such earlier date as the Committee may determine) to which such agreement relates.

**7. GRANT OF OPTION ON ENROLLMENT.** Becoming a Participant with respect to an Offering Period will constitute the grant (as of the Offering Date) by the Company to such Participant of an option to purchase on the Purchase Date up to that number of shares of Common Stock of the Company determined by a fraction, the numerator of which is the amount accumulated in such Participant's Contribution account during such Purchase Period and the denominator of which is the lower of (i) eighty-five percent (85%) of the Fair Market Value of a share of Common Stock on the Offering Date (but in no event less than the par value of a share of the Common Stock), or (ii) eighty-five percent (85%) of the Fair Market Value of a share of the Common Stock on the Purchase Date; provided, however, that for the Purchase Period within the initial Offering Period the numerator shall be fifteen percent (15%) of the Participant's compensation for such Purchase Period, or such lower percentage as determined by the Committee prior to the start of the Offering Period, and provided, further, that the number of shares of Common Stock subject to any option granted pursuant to this Plan shall not exceed the lesser of (x) the maximum number of shares set by the Committee pursuant to Section 10(b) below with respect to the applicable Purchase Date, or (y) the maximum number of shares which may be purchased pursuant to Section 10(a) below with respect to the applicable Purchase Date.

**8. PURCHASE PRICE.** The Purchase Price per share at which a share of Common Stock will be sold in any Offering Period shall be eighty-five percent (85%) of the lesser of:

- (a) The Fair Market Value on the Offering Date; or
- (b) The Fair Market Value on the Purchase Date.

#### **9. PAYMENT OF PURCHASE PRICE; CONTRIBUTION CHANGES; SHARE ISSUANCES.**

(a) The Purchase Price shall be accumulated by regular payroll deductions made during each Offering Period, unless the Committee determines with respect to categories of Participants outside the United States that Contributions may be made in another form due to local legal requirements. The Contributions are made as a percentage of the Participant's Compensation in one percent (1%) increments

not less than one percent (1%), nor greater than fifteen percent (15%) or such lower limit set by the Committee. "**Compensation**" shall mean base salary (or in foreign jurisdictions, equivalent cash compensation); however, the Committee may at any time prior to the beginning of an Offering Period determine that for that and future Offering Periods, Compensation shall mean all cash compensation reported on the employee's Form W-2 or corresponding local country tax return, including without limitation base salary or regular hourly wages, bonuses, incentive compensation, commissions, overtime, shift premiums, and draws against commissions. For purposes of determining a Participant's Compensation, any election by such Participant to reduce his or her regular cash remuneration under Sections 125 or 401(k) of the Code (or in foreign jurisdictions, equivalent salary deductions) shall be treated as if the Participant did not make such election. Contributions shall commence on the first payday following the last Purchase Date (with respect to the initial Offering Period, as soon as practicable following the effective date of filing with the U.S. Securities and Exchange Commission a securities registration statement for the Plan) and shall continue to the end of the Offering Period unless sooner altered or terminated as provided in this Plan. Notwithstanding the foregoing, the terms of any sub-plan may permit matching shares without the payment of any purchase price.

(b) A Participant may decrease the rate of Contributions during an Offering Period by filing with the Company or a third party designated by the Company a new authorization for Contributions, with the new rate to become effective no later than the second payroll period commencing after the Company's receipt of the authorization and continuing for the remainder of the Offering Period unless changed as described below. A decrease in the rate of Contributions may be made once during an Offering Period, but up to twice during the initial Offering Period, or more frequently under rules determined by the Committee. A Participant may increase or decrease the rate of Contributions for any subsequent Offering Period by filing with the Company or a third party designated by the Company a new authorization for Contributions prior to the beginning of such Offering Period, or such other time period as specified by the Committee.

(c) A Participant may reduce his or her Contribution percentage to zero during an Offering Period by filing with the Company or a third party designated by the Company a request for cessation of Contributions. Such reduction shall be effective beginning no later than the second payroll period after the Company's receipt of the request and no further Contributions will be made for the duration of the Offering Period. Contributions credited to the Participant's account prior to the effective date of the request shall be used to purchase shares of Common Stock in accordance with Subsection (e) below. A reduction of the Contribution percentage to zero shall be treated as such Participant's withdrawal from such Offering Period and the Plan, effective as of the day after the next Purchase Date following the filing date of such request with the Company.

(d) All Contributions made for a Participant are credited to his or her book account under this Plan and are deposited with the general funds of the Company, except to the extent local legal restrictions outside the United States require segregation of such Contributions. No interest accrues on the Contributions, except to the extent required due to local legal requirements. All Contributions received or held by the Company may be used by the Company for any corporate purpose, and the Company shall not be obligated to segregate such Contributions, except to the extent necessary to comply with local legal requirements outside the United States.

(e) On each Purchase Date, so long as this Plan remains in effect and provided that the Participant has not submitted a signed and completed withdrawal form before that date which notifies the Company that the Participant wishes to withdraw from that Offering Period under this Plan and have all Contributions accumulated in the account maintained on behalf of the Participant as of that date returned to the Participant, the Company shall apply the funds then in the Participant's account to the purchase of whole shares of Common Stock reserved under the option granted to such Participant with respect to the Offering Period to the extent that such option is exercisable on the Purchase Date. The Purchase Price per share for such automatic purchase shall be as specified in Section 8 of this Plan. Any fractional share, as calculated under this Subsection (e), shall be rounded down to the next lower whole share, unless the Committee determines with respect to all Participants that any fractional share shall be credited as a fractional share. Any amount remaining in a Participant's account on a Purchase Date that is less than the amount necessary to purchase a full share of Common Stock shall be returned to the Participant, without interest (except to the

extent necessary to comply with local legal requirements outside the United States); however, the Committee may provide that such amounts may be carried forward into the next Purchase Period or Offering Period, as the case may be. In the event that this Plan has been oversubscribed, all funds not used to purchase shares on the Purchase Date shall be returned to the Participant, without interest (except to the extent required due to local legal requirements outside the United States). No Common Stock shall be purchased on a Purchase Date on behalf of any employee whose participation in this Plan has terminated prior to such Purchase Date, except to the extent required due to local legal requirements outside the United States.

(f) As promptly as practicable after the Purchase Date, the Company shall issue shares for the Participant's benefit representing the shares purchased upon exercise of his or her option to purchase shares hereunder.

(g) During a Participant's lifetime, his or her option to purchase shares hereunder is exercisable only by him or her. The Participant will have no interest or voting right in shares covered by his or her option until such option has been exercised.

(h) To the extent required by applicable federal, state, local or foreign law, a Participant shall make arrangements satisfactory to the Company and the Participating Corporation employing the Participant for the satisfaction of any withholding tax obligations that arise in connection with the Plan. The Company or any Subsidiary or Affiliate, as applicable, may withhold, by any method permissible under the applicable law, the amount necessary for the Company or Subsidiary or Affiliate, as applicable, to meet applicable withholding obligations, including any withholding required to make available to the Company or Subsidiary or Affiliate, as applicable, any tax deductions or benefits attributable to the sale or early disposition of shares of Common Stock by a Participant. The Company shall not be required to issue any shares of Common Stock under the Plan until such obligations are satisfied.

#### **10. LIMITATIONS ON SHARES TO BE PURCHASED.**

(a) Any other provision of the Plan notwithstanding, no Participant shall purchase Common Stock with a Fair Market Value in excess of the following limit:

(i) In the case of Common Stock purchased during an Offering Period that commenced in the current calendar year, the limit shall be equal to (A) \$25,000 minus (B) the Fair Market Value of the Common Stock that the Participant previously purchased in the current calendar year (under this Plan and all other employee stock purchase plans of the Company or any Parent or Subsidiary).

(ii) In the case of Common Stock purchased during an Offering Period that commenced in the immediately preceding calendar year, the limit shall be equal to (A) \$50,000 minus (B) the Fair Market Value of the Common Stock that the Participant previously purchased (under this Plan and all other employee stock purchase plans of the Company or any Parent or Subsidiary) in the current calendar year and in the immediately preceding calendar year.

For purposes of this Subsection (a), the Fair Market Value of Common Stock shall be determined in each case as of the beginning of the Offering Period in which such Common Stock is purchased. Employee stock purchase plans not described in Section 423 of the Code shall be disregarded. If a Participant is precluded by this Subsection (a) from purchasing additional Common Stock under the Plan, then his or her Contributions shall automatically be discontinued and shall automatically resume at the beginning of the earliest Purchase Period that will end in the next calendar year (if he or she then is an eligible employee), provided that when the Company automatically resumes such Contributions, the Company must apply the rate in effect immediately prior to such suspension.

(b) In no event shall a Participant be permitted to purchase more than 2,000 shares on any one Purchase Date, or such lesser number as the Committee shall determine. If a lower limit is set under this Subsection (b), then all Participants will be notified of such limit prior to the commencement of the next Offering Period for which it is to be effective.

(c) If the number of shares to be purchased on a Purchase Date by all Participants exceeds the number of shares then available for issuance under this Plan, then the Company will make a pro rata allocation of the remaining shares in as uniform a manner as shall be reasonably practicable and as the Committee shall determine to be equitable. In such event, the Company will give notice of such reduction of the number of shares to be purchased under a Participant's option to each Participant affected.

(d) Any Contributions accumulated in a Participant's account that are not used to purchase stock due to the limitations in this Section 10, and not subject to the automatic purchase provision of Section 9(e), shall be returned to the Participant as soon as practicable after the end of the applicable Purchase Period, without interest (except to the extent required due to local legal requirements outside the United States).

#### **11. WITHDRAWAL.**

(a) Each Participant may withdraw from an Offering Period under this Plan pursuant to a method specified for such purpose by the Company. Such withdrawal may be elected at any time prior to the end of an Offering Period, or such other time period as specified by the Committee.

(b) Upon withdrawal from this Plan, the accumulated Contributions shall be returned to the withdrawn Participant, without interest (except to the extent required due to local legal requirements outside the United States), and his or her interest in this Plan shall terminate. In the event a Participant voluntarily elects to withdraw from this Plan, he or she may not resume his or her participation in this Plan during the same Offering Period, but he or she may participate in any Offering Period under this Plan which commences on a date subsequent to such withdrawal by filing a new authorization for Contributions in the same manner as set forth in Section 6 above for initial participation in this Plan.

**12. TERMINATION OF EMPLOYMENT.** Termination of a Participant's employment for any reason, including retirement, death, disability, or the failure of a Participant to remain an eligible employee of the Company or of a Participating Corporation, immediately terminates his or her participation in this Plan (except as required due to local legal requirements outside the United States). In such event, accumulated Contributions credited to the Participant's account will be returned to him or her or, in the case of his or her death, to his or her legal representative, without interest (except to the extent required due to local legal requirements outside the United States). For purposes of this Section 12, an employee will not be deemed to have terminated employment or failed to remain in the continuous employ of the Company or of a Participating Corporation in the case of sick leave, military leave, or any other leave of absence approved by the Company; provided that such leave is for a period of not more than ninety (90) days or reemployment upon the expiration of such leave is guaranteed by contract or statute. The Company will have sole discretion to determine whether a Participant has terminated employment and the effective date on which the Participant terminated employment, regardless of any notice period or garden leave required under local law.

**13. RETURN OF CONTRIBUTIONS.** In the event a Participant's interest in this Plan is terminated by withdrawal, termination of employment or otherwise, or in the event this Plan is terminated by the Board, the Company shall deliver to the Participant all accumulated Contributions credited to such Participant's account. No interest shall accrue on the Contributions of a Participant in this Plan (except to the extent required due to local legal requirements outside the United States).

**14. CAPITAL CHANGES.** If the number of outstanding shares is changed by a stock dividend, recapitalization, stock split, reverse stock split, subdivision, combination, reclassification or similar change in the capital structure of the Company, without consideration, then the Committee shall adjust the number and class of Common Stock that may be delivered under the Plan, the Purchase Price per share and the number of shares of Common Stock covered by each option under the Plan which has not yet been exercised, and the numerical limits of Sections 2 and 10 shall be proportionately adjusted, subject to any required action by the Board or the stockholders of the Company and in compliance with the applicable securities laws; provided that fractions of a share will not be issued.

**15. NONASSIGNABILITY.** Neither Contributions credited to a Participant's account nor any rights with regard to the exercise of an option or to receive shares under this Plan may be assigned, transferred, pledged or otherwise disposed of in any way (other than by will, the laws of descent and distribution or as provided in Section 22 below) by the Participant. Any such attempt at assignment, transfer, pledge or other disposition shall be void and without effect.

**16. USE OF PARTICIPANT FUNDS AND REPORTS.** The Company may use all Contributions received or held by it under the Plan for any corporate purpose, and the Company will not be required to segregate Participant Contributions (except to the extent required due to local legal requirements outside the United States). Until shares are issued, Participants will only have the rights of an unsecured creditor unless otherwise required under local law. Each Participant shall receive promptly after the end of each Purchase Period a report of his or her account setting forth the total Contributions accumulated, the number of shares purchased, the per share price thereof and the remaining cash balance, if any, carried forward to the next Purchase Period or Offering Period, as the case may be.

**17. NOTICE OF DISPOSITION.** Each U.S. taxpayer Participant shall notify the Company in writing if the Participant disposes of any of the shares purchased in any Offering Period pursuant to this Plan if such disposition occurs within two (2) years from the Offering Date or within one (1) year from the Purchase Date on which such shares were purchased (the "**Notice Period**"). The Company may, at any time during the Notice Period, place a legend or legends on any certificate representing shares acquired pursuant to this Plan requesting the Company's transfer agent to notify the Company of any transfer of the shares. The obligation of the Participant to provide such notice shall continue notwithstanding the placement of any such legend on the certificates.

**18. NO RIGHTS TO CONTINUED EMPLOYMENT.** Neither this Plan nor the grant of any option hereunder shall confer any right on any employee to remain in the employ of the Company or any Participating Corporation, or restrict the right of the Company or any Participating Corporation to terminate such employee's employment.

**19. EQUAL RIGHTS AND PRIVILEGES.** All eligible employees granted an option under the Section 423 Component of this Plan shall have equal rights and privileges with respect to this Plan or within any separate offering under the Plan so that this Plan qualifies as an "employee stock purchase plan" within the meaning of Section 423 or any successor provision of the Code and the related regulations. Any provision of this Plan which is inconsistent with Section 423 or any successor provision of the Code, without further act or amendment by the Company, the Committee or the Board, shall be reformed to comply with the requirements of Section 423. This Section 19 shall take precedence over all other provisions in this Plan.

**20. NOTICES.** All notices or other communications by a Participant to the Company under or in connection with this Plan shall be deemed to have been duly given when received in the form specified by the Company at the location, or by the person, designated by the Company for the receipt thereof.

**21. TERM; STOCKHOLDER APPROVAL.** The amendment and restatement of the Plan shall be approved by the stockholders of the Company, in any manner permitted by applicable corporate law, within twelve (12) months before or after the date this amendment and restatement of the Plan is adopted by the Board. The amendment and restatement of the Plan will become effective upon approval by stockholders at the 2018 Annual Meeting of Stockholders. No purchase of shares that are subject to such stockholder approval before becoming available under this Plan shall occur prior to stockholder approval of such shares and the Board or Committee may delay any Purchase Date and postpone the commencement of any Offering Period subsequent to such Purchase Date as deemed necessary or desirable to obtain such approval (provided that if a Purchase Date would occur more than twenty-seven (27) months after commencement of the Offering Period to which it relates, then such Purchase Date shall not occur and instead such Offering Period shall terminate without the purchase of such shares and Participants in such Offering Period shall be refunded their Contributions without interest). If the amendment and restatement of the Plan is not approved by the stockholders of the Company within twelve (12) months before or after the date this amendment and restatement of the Plan is adopted by the Board, then it shall be null and void

and the Plan shall continue in effect without the terms approved in the amendment and restatement. This Plan shall continue until the earlier to occur of (a) termination of this Plan by the Board (which termination may be effected by the Board at any time pursuant to Section 25 below), (b) issuance of all of the shares of Common Stock reserved for issuance under this Plan, or (c) the tenth anniversary of the Effective Date under the Plan.

## **22. DESIGNATION OF BENEFICIARY.**

(a) Unless otherwise determined by the Committee, a Participant may file a written designation of a beneficiary who is to receive any cash from the Participant's account under this Plan in the event of such Participant's death prior to a Purchase Date. Such form shall be valid only if it was filed with the Company at the prescribed location before the Participant's death.

(b) If authorized by the Company, such designation of beneficiary may be changed by the Participant at any time by written notice filed with the Company at the prescribed location before the Participant's death. In the event of the death of a Participant and in the absence of a beneficiary validly designated under this Plan who is living at the time of such Participant's death, the Company shall deliver such cash to the executor or administrator of the estate of the Participant or to the legal heirs of the Participant.

**23. CONDITIONS UPON ISSUANCE OF SHARES; LIMITATION ON SALE OF SHARES.** Shares shall not be issued with respect to an option unless the exercise of such option and the issuance and delivery of such shares pursuant thereto shall comply with all applicable provisions of law, domestic or foreign, including, without limitation, the U.S. Securities Act of 1933, as amended, the U.S. Securities Exchange Act of 1934, as amended, the rules and regulations promulgated thereunder, and the requirements of any stock exchange or automated quotation system upon which the shares may then be listed, exchange control restrictions and/or securities law restrictions outside the United States, and shall be further subject to the approval of counsel for the Company with respect to such compliance. Shares may be held in trust or subject to further restrictions as permitted by any subplan.

**24. APPLICABLE LAW.** The Plan shall be governed by the substantive laws (excluding the conflict of laws rules) of the State of Delaware.

**25. AMENDMENT OR TERMINATION.** The Committee, in its sole discretion, may amend, suspend, or terminate the Plan, or any part thereof, at any time and for any reason. Unless otherwise required by applicable law, if the Plan is terminated, the Committee, in its discretion, may elect to terminate all outstanding Offering Periods either immediately or upon completion of the purchase of shares of Common Stock on the next Purchase Date (which may be sooner than originally scheduled, if determined by the Committee in its discretion), or may elect to permit Offering Periods to expire in accordance with their terms (and subject to any adjustment pursuant to Section 14). If an Offering Period is terminated prior to its previously-scheduled expiration, all amounts then credited to Participants' accounts for such Offering Period, which have not been used to purchase shares of Common Stock, shall be returned to those Participants (without interest thereon, except as otherwise required under local laws) as soon as administratively practicable. Further, the Committee will be entitled to change the Purchase Periods and Offering Periods, limit the frequency and/or number of changes in the amount contributed during an Offering Period, establish the exchange ratio applicable to amounts contributed in a currency other than U.S. dollars, permit payroll withholding in excess of the amount designated by a Participant in order to adjust for delays or mistakes in the administration of the Plan, establish reasonable waiting and adjustment periods and/or accounting and crediting procedures to ensure that amounts applied toward the purchase of Common Stock for each Participant properly correspond with amounts contributed from the Participant's base salary and other eligible compensation, and establish such other limitations or procedures as the Committee determines in its sole discretion advisable which are consistent with the Plan. Such actions will not require stockholder approval or the consent of any Participants. However, no amendment shall be made without approval of the stockholders of the Company (obtained in accordance with Section 21 above) within

twelve (12) months of the adoption of such amendment (or earlier if required by Section 21) if such amendment would: (a) increase the number of shares that may be issued under this Plan; or (b) change the designation of the employees (or class of employees) eligible for participation in this Plan. In addition, in the event the Board or Committee determines that the ongoing operation of the Plan may result in unfavorable financial accounting consequences, the Board or Committee may, in its discretion and, to the extent necessary or desirable, modify, amend or terminate the Plan to reduce or eliminate such accounting consequences including, but not limited to: (i) amending the definition of compensation, including with respect to an Offering Period underway at the time; (ii) altering the Purchase Price for any Offering Period including an Offering Period underway at the time of the change in Purchase Price; (iii) shortening any Offering Period by setting a Purchase Date, including an Offering Period underway at the time of the Committee's action; (iv) reducing the maximum percentage of Compensation a participant may elect to set aside as Contributions; and (v) reducing the maximum number of shares a Participant may purchase during any Offering Period. Such modifications or amendments will not require approval of the stockholders of the Company or the consent of any Participants.

**26. CORPORATE TRANSACTIONS.** In the event of a Corporate Transaction, the Offering Period for each outstanding right to purchase Common Stock will be shortened by setting a new Purchase Date and will end on the new Purchase Date. The new Purchase Date shall occur on or prior to the consummation of the Corporate Transaction, as determined by the Board or Committee, and the Plan shall terminate on the consummation of the Corporate Transaction.

**27. CODE SECTION 409A; TAX QUALIFICATION.**

(a) Options granted under the Plan generally are exempt from the application of Section 409A of the Code. However, options granted to U.S. taxpayers which are not intended to meet the Code Section 423 requirements are intended to be exempt from the application of Section 409A of the Code under the short-term deferral exception and any ambiguities shall be construed and interpreted in accordance with such intent. Subject to Subsection (b), options granted to U.S. taxpayers outside of the Code Section 423 requirements shall be subject to such terms and conditions that will permit such options to satisfy the requirements of the short-term deferral exception available under Section 409A of the Code, including the requirement that the shares of Common Stock subject to an option be delivered within the short-term deferral period. Subject to Subsection (b), in the case of a Participant who would otherwise be subject to Section 409A of the Code, to the extent the Committee determines that an option or the exercise, payment, settlement or deferral thereof is subject to Section 409A of the Code, the option shall be granted, exercised, paid, settled or deferred in a manner that will comply with Section 409A of the Code, including Treasury regulations and other interpretive guidance issued thereunder, including without limitation any such regulations or other guidance that may be issued after the Effective Date. Notwithstanding the foregoing, the Company shall have no liability to a Participant or any other party if the option that is intended to be exempt from or compliant with Section 409A of the Code is not so exempt or compliant or for any action taken by the Committee with respect thereto.

(b) Although the Company may endeavor to (i) qualify an option for favorable tax treatment under the laws of the United States or jurisdictions outside of the United States or (ii) avoid adverse tax treatment (e.g., under Section 409A of the Code), the Company makes no representation to that effect and expressly disavows any covenant to maintain favorable or avoid unfavorable tax treatment, notwithstanding anything to the contrary in this Plan, including Subsection (a). The Company shall be unconstrained in its corporate activities without regard to the potential negative tax impact on Participants under the Plan.

**28. DEFINITIONS.**

(a) **"Affiliate"** means any entity, other than a Subsidiary or Parent, (i) that, directly or indirectly, is controlled by, controls or is under common control with, the Company and (ii) in which the Company has a significant equity interest, in either case as determined by the Committee, whether now or hereafter existing.

(b) **"Board"** shall mean the Board of Directors of the Company.

(c) "**Code**" shall mean the U.S. Internal Revenue Code of 1986, as amended.

(d) "**Committee**" shall mean the Compensation Committee of the Board that consists exclusively of one or more members of the Board appointed by the Board.

(e) "**Common Stock**" shall mean the common stock of the Company.

(f) "**Company**" shall mean Aeglea Biotherapeutics, Inc.

(g) "**Contributions**" means payroll deductions taken from a Participant's Compensation and used to purchase shares of Common Stock under the Plan and, to the extent payroll deductions are not permitted by applicable laws (as determined by the Committee in its sole discretion) contributions by other means, provided, however, that allowing such other contributions does not jeopardize the qualification of the Plan as an "employee stock purchase plan" under Section 423 of the Plan.

(h) "**Corporate Transaction**" means the occurrence of any of the following events:

(i) any "person" (as such term is used in Sections 13(d) and 14(d) of the Exchange Act) becomes the "beneficial owner" (as defined in Rule 13d-3 of the Exchange Act), directly or indirectly, of securities of the Company representing fifty percent (50%) or more of the total voting power represented by the Company's then outstanding voting securities; or (ii) the consummation of the sale or disposition by the Company of all or substantially all of the Company's assets; or (iii) the consummation of a merger or consolidation of the Company with any other corporation, other than a merger or consolidation which would result in the voting securities of the Company outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity or its parent) at least fifty percent (50%) of the total voting power represented by the voting securities of the Company or such surviving entity or its parent outstanding immediately after such merger or consolidation.

(i) "**Effective Date**" shall mean the date on which the Registration Statement covering the initial public offering of the shares of Common Stock is declared effective by the U.S. Securities and Exchange Commission.

(j) "**Fair Market Value**" shall mean, as of any date, the value of a share of Common Stock determined as follows:

(1) if such Common Stock is then quoted on the Nasdaq Global Select Market, the Nasdaq Global Market or the Nasdaq Capital Market (collectively, the "**Nasdaq Market**"), its closing price on the Nasdaq Market on the date of determination, or if there are no sales for such date, then the last preceding business day on which there were sales, as reported in *The Wall Street Journal* or such other source as the Board or the Committee deems reliable; or

(2) if such Common Stock is publicly traded and is then listed on a national securities exchange, its closing price on the date of determination on the principal national securities exchange on which the Common Stock is listed or admitted to trading as reported in *The Wall Street Journal* or such other source as the Board or the Committee deems reliable; or

(3) if such Common Stock is publicly traded but is neither quoted on the Nasdaq Market nor listed or admitted to trading on a national securities exchange, the average of the closing bid and asked prices on the date of determination as reported in *The Wall Street Journal* or such other source as the Board or the Committee deems reliable; or

(4) with respect to the initial Offering Period, Fair Market Value on the Offering Date shall be the price at which shares of Common Stock are offered to the public pursuant to the Registration Statement covering the initial public offering of shares of Common Stock; or

(5) if none of the foregoing is applicable, by the Board or the Committee in good faith.

(k) "**IPO**" shall mean the initial public offering of Common Stock.

(l) "**Non-Section 423 Component**" means the part of the Plan which is not intended to meet the requirements set forth in Section 423 of the Code.

(m) "**Notice Period**" shall mean within two (2) years from the Offering Date or within one (1) year from the Purchase Date on which such shares were purchased.

(n) "**Offering Date**" shall mean the first business day of each Offering Period. However, for the initial Offering Period the Offering Date shall be the Effective Date.

(o) "**Offering Period**" shall mean a period with respect to which the right to purchase Common Stock may be granted under the Plan, as determined by the Committee pursuant to Section 5(a).

(p) "**Parent**" shall have the same meaning as "parent corporation" in Sections 424(e) and 424(±) of the Code.

(q) "**Participant**" shall mean an eligible employee who meets the eligibility requirements set forth in Section 4 and who is either automatically enrolled in the initial Offering Period or who elects to participate in this Plan pursuant to Section 6(b).

(r) "**Participating Corporation**" shall mean any Parent, Subsidiary or Affiliate that the Committee designates from time to time as eligible to participate in this Plan. For purposes of the Section 423 Component, only the Parent and Subsidiaries may be Participating Corporations, provided, however, that at any given time a Parent or Subsidiary that is a Participating Corporation under the Section 423 Component shall not be a Participating Corporation under the Non-Section 423 Component.

The Committee may provide that any Participating Corporation shall only be eligible to participate in the Non-Section 423 Component.

(s) "**Plan**" shall mean this Aeglea BioTherapeutics, Inc. 2016 Employee Stock Purchase Plan, as may be amended from time to time.

(t) "**Purchase Date**" shall mean the last business day of each Purchase Period.

(u) "**Purchase Period**" shall mean a period during which Contributions may be made toward the purchase of Common Stock under the Plan, as determined by the Committee pursuant to Section S(b).

(v) "**Purchase Price**" shall mean the price at which Participants may purchase shares of Common Stock under the Plan, as determined pursuant to Section 8.

(w) "**Section 423 Component**" means the part of the Plan, which excludes the Non- Section 423 Component, pursuant to which options to purchase shares of Common Stock under the Plan that satisfy the requirements for "employee stock purchase plans" set forth in Section 423 of the Code may be granted to eligible employees.

(x) "**Subsidiary**" shall have the same meaning as "subsidiary corporation" in Sections 424(e) and 424(f) of the Code.

[\*] Certain confidential information contained in this document, marked by brackets, has been omitted and filed separately with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934, as amended.

**Amended and Restated Patent License Agreement  
Agreement No. PM1401501**

This Amended and Restated Patent License Agreement (“Patent License Agreement”) is between the Licensor and the Licensee identified below (collectively, “Parties”, or singly, “Party”).

**Background**

Licensor owns or controls Patent Rights. Licensee desires to secure the right and license to use, develop, manufacture, market, and commercialize the Patent Rights. Licensor has determined that such use, development, and commercialization of the Patent Rights is in the public’s best interest and is consistent with Licensor’s educational and research missions and goals. Licensor desires to have the Patent Rights developed and used for the benefit of Licensee, the inventors, Licensor, and the public.

Licensor has previously entered into two separate license agreements with subsidiaries of Aeglea BioTherapeutics, Inc. (“Aeglea”). These license agreements are between Licensor and AECCase, LLC (PM1401501), and AEMase, LLC (PM140161), respectively, both effective December 24, 2013 (the “Prior Agreements”). Licensor and Aeglea wish to amend certain terms of the Prior Agreements and to combine the two Prior Agreements into this single Amended and Restated Patent License Agreement. This Amended and Restated Patent License Agreement will amend, restate, and supersede the Prior Agreements in all respects.

NOW, THEREFORE, in consideration of the mutual covenants and premises herein contained, the Parties hereby agree as follows:

The terms and conditions of this Patent License Agreement attached hereto as Exhibit A are incorporated herein by reference in their entirety (the “Terms and Conditions”). In the event of a conflict between provisions of this Patent License Agreement and the Terms and Conditions, the provisions in this Patent License Agreement shall govern. Unless defined in this Patent License Agreement, capitalized terms used in this Patent License Agreement shall have the meanings given to them in the Terms and Conditions.

The section numbers used in the left hand column in the table below correspond to the section numbers in the Terms and Conditions.

1.	<b>Definitions</b>	
	<b>Effective Date</b>	Date of last signature below
	<b>Licensor</b>	The University of Texas at Austin, on behalf of the Board of Regents of the University of Texas System, an agency of the State of Texas, whose address is 3925 W. Braker Lane, Suite 1.9A (R3500), Austin, Texas 78759.

<b>Licensee</b>	Aeglea BioTherapeutics, Inc.
<b>Contract Year and Contract Quarters</b>	Contract Year is 12-month period ending on December 31 and Contract Quarters are 3-month periods ending on March 31, June 30, Sept. 30, Dec. 31
<b>Territory</b>	World-wide
<b>Field</b>	All fields

<b>Patent Rights</b>					
<b>App. No./ Date of Filing</b>	<b>Title</b>	<b>Inventor(s)</b>	<b>Jointly Owned? (Y/N; if Y, with whom?)</b>	<b>Prosecution Counsel</b>	
US61/871,727 filed 8/29/2013	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
US61/948,106 filed 03/05/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
US14/472,779 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
South Korea 10- 2016-7008 299 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
PCT/US2014/0 53374 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
JP filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
Israel 244263 I filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
Europe 14839001.6 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
China 201480054224.9 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
Canada 2,922,557 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
Australia 2014312168 filed 08/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC	
US61/871,768 filed 08/29/2013	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (614 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC	

Patent Rights				
App. No./ Date of Filing	Title	Inventor(s)	Jointly Owned? (Y/N; if Y, with whom?)	Prosecution Counsel
US14/472,750 filed 08/29/2013	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
South Korea 10- 2016-7007-045 filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
PCT/U52014/ 053359 filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
JP filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Israel 244261 filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Europe 14841106.9 filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
China 20140050681.0 filed 08.29.2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Canada 2,922,550 filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Australia 2014312159 filed 08/29/2014	Engineered Human Methionine Gamma Lyase Enzymes and Pharmacological Preparations Thereof (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
[*]	[*]	[*]	[*]	[*]
[*]	[*]	[*]	[*]	[*]
USPTO Entity Status as of Effective Date		Check one box: Small <input type="checkbox"/> Large <input type="checkbox"/>		

**\*Confidential Treatment Requested.**

2.4	Diligence Milestones	
Diligence Milestones and deadlines (see Section 20.1)	Diligence Milestones	Deadlines
	[*]	[*]
	[*]	[*]
	[*]	[*]
	[*]	[*]
	[*]	[*]
	[*]	[*]
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	[*]	[*]
	[*]	[*]
	[*]	[*]
	[*]	[*]
	[*]	[*]

**\*Confidential Treatment Requested.**

<b>3.</b>	<b>Compensation</b>		
<b>3.1(a)</b>	<b>Patent expenses due upon Effective Date</b>	<b>Amount</b>	<b>Based on invoices received as of:</b>
		[*]	[*]

<b>3.1(b)</b>	<b>Milestone fees</b>		
		<b>Milestone Events</b>	<b>Milestone Fees</b>
		[*]	[*]
		[*]	[*]
		[*]	[*]
		[*]	[*]
		[*]	[*]
		[*]	[*]
		7.Obtain Regulatory Approval in any country [*]	\$5,000,000
		8.Obtain Regulatory Approval in any country [*]	\$5,000,000
		9.Obtain Regulatory Approval for an additional indication in any country [*]	\$500,000
		10.Obtain Regulatory Approval for an additional indication in any country [*]	\$500,000

**\*Confidential Treatment Requested.**

<b>3.1(c)</b>	<b>Scheduled license fee payments</b>	[*]
<b>3.1(d)</b>	<b>Sublicense Fees</b>	25% of Non-Royalty Sublicensing Consideration from a Sublicense Agreement fully signed before [*] 20% of Non-Royalty Sublicensing Consideration from a Sublicense Agreement fully signed on or after [*] and before [*] 15% of Non-Royalty Sublicensing Consideration from a Sublicense Agreement fully signed on or after [*] and before [*] 6.5% of Non-Royalty Sublicensing Consideration Agreement signed on or after [*]
<b>3.1(e)</b>	<b>Assignment Fee</b>	[*]
<b>3.2</b>	<b>Running royalty rate (applies to Net Product Sales by Licensee, Affiliates and Sublicensees)</b>	[*]

<b>18.</b>	<b>Contact Information</b>
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Licensee Contacts	Licensor Contacts
<p>Contact for Notice:            Attn: David G. Lowe            Aeglea BioTherapeutics, Inc.            901 S. MoPac Expressway            Barton Oaks Plaza One            Suite 250            Austin, TX 78746            Fax: (512) 872-5121            Phone: (512) 942-2935            E-mail: <a href="mailto:David@aegleabio.com">David@aegleabio.com</a></p> <p>Accounting contact:            Attn: Charles York            Aeglea BioTherapeutics, Inc.            901 S. MoPac Expressway            Barton Oaks Plaza One            Suite 250            Austin, TX 78746            Fax: (512) 872-5121            Phone: (512) 942-2935            E-mail: <a href="mailto:cyork@aegleabio.com">cyork@aegleabio.com</a></p> <p>Patent prosecution contact:            Attn: Head of Business and            Corporate Development            Aeglea BioTherapeutics, Inc.            901 S. MoPac Expressway            Barton Oaks Plaza One            Suite 250            Austin, TX 78746            Fax: (512) 872-5121            Phone: (512) 942-2935            E-mail: <a href="mailto:David@aegleabio.com">David@aegleabio.com</a>  <a href="mailto:contracts@aegleabio.com">contracts@aegleabio.com</a></p> <p>With a copy to:            Attn: Erin Thomson            Vinson &amp; Elkins LLP            2801 Via Fortuna            Suite 100            Austin, TX 78746            Phone: (512) 542-8762            E-mail: <a href="mailto:ethomson@velaw.com">ethomson@velaw.com</a></p>	<p>Contact for Notice:            Attn: Contract Manager            3925 W. Braker Lane, Suite 1.9A (R3500)            Austin, TX 78759            Fax: 512 475-6894            Phone: 512 471-2995            E-mail: <a href="mailto:licensing@otc.utexas.edu">licensing@otc.utexas.edu</a></p> <p>Payment and reporting contact:            Checks payable to "The University of Texas at Austin"            Attn: Accounting            3925 W. Braker Lane, Suite 1.9A (R3500)            Austin, TX 78759            Fax: 512 475-6894            Phone: 512 471-2995            E-mail: <a href="mailto:accounting@otc.utexas.edu">accounting@otc.utexas.edu</a></p> <p>Patent prosecution contact:            Attn: Patents            3925 W. Braker Lane, Suite 1.9A (R3500)            Austin, TX 78759            Fax: 512 475-6894            Phone: 512 471-2995            E-mail: <a href="mailto:patents@otc.utexas.edu">patents@otc.utexas.edu</a></p>

For Licensor Administrative Purposes Only
<p>Changes to Standard Form Terms and Conditions            Yes</p>

**20. Special Provision.** The Parties hereby agree to the following special provisions set forth in this Section 20 with respect to this Patent License Agreement.

**20.1 Diligence Milestones.**

**20.1.1** Upon written request from Licensee to Licensor given prior to the scheduled deadline date to achieve a particular Diligence Milestone set forth in Section 2.4, Licensee may request a [\*] extension of said Diligence Milestone deadline date; and said request shall be accompanied by evidence that demonstrates to Licensor's reasonable satisfaction that Licensee (and/or its Affiliates and Sublicensees) have been devoting continued diligent efforts to achieve said Diligence Milestone; and Licensor shall grant the requested extension if Licensor approves the evidence and efforts, which approval will not be withheld unreasonably.

\*Confidential Treatment Requested.

**20.1.2** If a first extension has been granted pursuant to Section 20.1.1 for a particular Diligence Milestone deadline, Licensee may request a [\*] extension for the same Diligence Milestone deadline, which request shall be made in accordance with the provisions set forth in Section 20.1.1; and if Licensor grants said request, Licensee shall pay [\*] to Licensor as consideration for this second extension, payable within thirty (30) days after Licensee receives written notice that Licensor is willing to grant the extension, which extension will not be effective if said consideration is not paid by said due date. Any failure to so pay said consideration shall not entitle Licensee to make a later delayed payment during any default cure period that is otherwise specified in this Agreement for curing other defaults.

**20.2** Prior to the assignment of this Patent License Agreement to a third party, "Non-Royalty Sublicensing Consideration" shall be as follows:

[\*]

After the assignment of this Patent License Agreement to a third party, "Non-Royalty Sublicensing Consideration" shall be defined as follows:

[\*]

**20.3** If the Parties mutually determine that the rights granted by this Patent License Agreement are essential to the Licensee's use of any University Invention arising under Sponsored Research Agreement UTA13-001113, then such University Invention shall be included in this Patent License Agreement, upon Licensee's payment to Licensor of a fee of [\*].

**20.4** This Patent License Agreement replaces and supersedes the Prior Agreements in all respects.

**21. No Other Promises and Agreements; Representation by Counsel.** Each Party expressly warrants and represents and does hereby state and represent that no promise or agreement which is not herein expressed has been made to such Party in executing this Patent License Agreement except those explicitly set forth herein and in the Terms and Conditions, and that such Party is not relying upon any statement or representation of the other Party or its representatives. Each Party is relying on its own judgment and has had the opportunity to be represented by legal counsel. Each Party hereby warrants and represents that it understands and

agrees to all terms and conditions set forth in this Patent License Agreement and said Terms and Conditions.

**22. Deadline for Execution by Licensee.** If this Patent License Agreement is executed first by the Licensor and is not executed by the Licensee and received by the Licensor at the address and in the manner set forth in Section 18 of the Terms and Conditions within thirty (30) days of the date of signature set forth under the Licensor's signature below, then this Patent License Agreement shall be null and void and of no further effect.

IN WITNESS WHEREOF, the Parties hereto have caused their duly authorized representatives to execute this Patent License Agreement.

**LICENSOR: THE UNIVERSITY OF TEXAS AT AUSTIN  
ON BEHALF OF TH BOARD OF REGENTS OF THE  
UNIVERSITY OF TEXAS SYSTEM**

**LICENSEE: Aeglea BioTherapeutics, Inc.**

By: /s/ Daniel W. Sharp, J.D.  
Daniel W. Sharp, J.D.  
Associate Vice President for Research and Director, Office of  
Technology Commercialization

By /s/ David G. Lowe  
David G. Lowe  
President and Chief Executive Officer

Date 1/30/17

Date 31 January 2017

EXHIBIT A  
TERMS AND CONDITIONS OF PATENT LICENSE

These Terms and Conditions of Patent License (“Terms and Conditions”) are incorporated by reference into the Patent License Agreement to which they are attached. All Section references in these Terms and Conditions shall be references to provisions in these Terms and Conditions unless explicitly stated otherwise.

1. **Definitions**

“**Affiliate**” of a Party means any person, corporation or other business entity which, directly or indirectly through one or more intermediaries, actually controls, is actually controlled by, or is under common control with that Party. As used in this paragraph, “control” means to possess, directly or indirectly, the power to affirmatively direct the management and policies of such person, corporation or other business entity, whether through ownership of at least fifty percent (50%) of the voting securities or by contract relating to voting rights or corporate governance.

“**Agreement**” means collectively (i) these Terms and Conditions, and (ii) the Patent License Agreement.

“**BLA**” means Biological License Application, as defined in the U.S. Federal Food, Drug and Cosmetic Act and the regulations promulgated thereunder, as well as any equivalent foreign application, registration or certification in the relevant country, such as a Marketing Approval Application in Europe, in each case with respect to a Licensed Product.

“**Change of Control**” with respect to any Party means the occurrence of any of the following events: (i) any “person” (as such term is used in Sections 13(d) and 14(d) of the Securities Exchange Act of 1934, as amended) is or becomes the “beneficial owner” (as defined in Rule 13d-3 under said Act) of securities representing fifty percent (50%) or more of the total voting power represented by such Party’s then -outstanding voting securities; or (ii) the consummation of (A) a merger or consolidation of such Party with any other corporation, other than a merger or consolidation which would result in the voting securities of such Party outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity or the entity that controls such surviving entity) at least fifty percent (50%) of the total voting power represented by the voting securities of such Party, such surviving entity or the entity that controls such Party or such surviving entity outstanding immediately after such merger or consolidation, or (iii) the sale or disposition by such Party, to a third party which is not an Affiliate of such Party, of all or substantially all such Party’s assets.

“**Commercially Reasonable Efforts**” means the expenditure of those efforts and resources used consistent with the usual practice of similarly situated companies in pursuing development or commercialization of its other similar pharmaceutical products with similar market potential and at a similar stage in development.

“**Contract Quarter**” means the three-month periods indicated as the Contract Quarter in Section 1 of the Patent License Agreement, or any stub period thereof at the commencement of the Agreement or the expiration or termination of the Agreement.

“**Contract Year**” means the 12-month periods indicated as the Contract Year in Section 1 of the Patent License Agreement, or any stub period thereof at the commencement of the Agreement or the expiration or termination of the Agreement.

“**Covered**” means that with respect to a Patent Right, but for the license granted under this Agreement, the use, manufacture, sale, offer for sale, development, commercialization or importation of the subject matter in question by an unlicensed entity would infringe a Valid Claim of a Patent Right.

“**Cumulative Received Capital**” means the total funding received by Licensee and its Affiliates after the Equity Financing which funding may be received in connection with any type of transaction, including, without limitation, grants, financings, licensing, research and development, and strategic collaborations.

“**Effective Date**” means the date indicated as the Effective Date in Section 1 of the Patent License Agreement.

“**Enzyme**” means [\*]

**\*Confidential Treatment Requested.**

“**Equity Financing**” means a transaction or series of related transactions in which Licensee and/or its Affiliates receive at least [\*] in cumulative proceeds from the sale of equity.

“**Fair Market Value**” means the cash consideration an unaffiliated, unrelated buyer would pay in an arm’s length sale of a substantially identical item sold in the same quantity, under the same terms, and at the same time and place.

“**Field**” means the field indicated as the Field identified in Section 1 of the Patent License Agreement.

“**Government**” means any agency, department, unit, or other instrumentality of the United States of America, or any foreign country, or any province, state, county, city or other political subdivision (including any supra-national agency such as in the European Union).

“**Gross Consideration**” means all cash and non-cash consideration (e.g., securities).

“**IND**” means an Investigational New Drug Application, as defined in the U.S. Federal Food, Drug and Cosmetic Act and the regulations promulgated thereunder, or comparable filing in a foreign jurisdiction, in each case with respect to a Licensed Product.

“**Licensed Process**” means a method or process whose practice or use is Covered by a Valid Claim.

“**Licensed Product**” means any product or component (i) whose manufacture, use, sale, offer for sale or import is Covered by any Valid Claim, or (ii) which is made using a Licensed Process.

“**Licensee**” means the Party identified as the Licensee in Section 1 of the Patent License Agreement.

“**Licensor**” means the Party identified as the Licensor in Section 1 of the Patent License Agreement.

“**Milestone Fees**” means all fees identified as Milestone Fees in Section 3.1(b) of the Patent License Agreement.

“**Net Product Sales**” means [\*]

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“**Patent License Agreement**” means the particular Patent License Agreement to which these Terms and Conditions are attached and incorporated into by reference.

“**Patent Rights**” means the Licensor’s rights in (a) the patents and patent applications listed in Section 1 of the Patent License Agreement; (b) all non-provisional patent applications that claim priority to any provisional application listed in Section 1 of the Patent License Agreement; and (c) all divisionals, continuations, and such claims of continuations-in-part as are entitled to claim priority to the aforesaid patents and/or patent applications, and all reissues, reexaminations, extensions of, and foreign counterparts; and (d) any patents that issue with respect to the aforesaid patent applications. From time to time during the term of the Agreement, upon written agreement by both Parties, Licensee and Licensor shall update the list of all patent applications and patents within the Patent Rights.

“**Phase II**” means a means a human clinical trial of a Licensed Product, including possibly pharmacokinetic studies, the principal purpose of which is to make a preliminary determination that such Product is safe in a patient population for its intended use and to obtain sufficient information about such Product’s efficacy to permit the design of further clinical trials, and generally consistent with 21 CFR § 312.21(b). Said trial may be conducted in any country.

“**Phase III**” means a human clinical trial of a Licensed Product, which trial is designed to: (a) establish that a Licensed Product is safe and efficacious for its intended use; (b) define warnings, precautions and adverse reactions that are associated with the Licensed Product in the dosage range to be prescribed; (c) support regulatory approval of such Licensed Product; and (d) be generally consistent with 21 CFR § 312.21(c). Said trial may be conducted in any country.

“**Prosecution Counsel**” means the law firm or attorney who is handling the prosecution of the Patent Rights. Prosecution Counsel as of the Effective Date is identified in Section 1 of the Patent License Agreement.

“**Quarterly Payment Deadline**” means the day that is ninety (90) days after the last day of any particular Contract Quarter.

“**Regulatory Approval**” means, with respect to any country, any and all approvals (including any applicable governmental price and reimbursement approvals), licenses, registrations, or authorizations of any Regulatory Authority necessary for the manufacture, use, storage, import, transport, marketing, and sale (including packaging and labeling) of a product for human use in a country, including approvals of BLAs and NDAs in the United States (and any foreign counterparts or equivalents).

“**Regulatory Authority**” means any federal, national, multinational, regional, state, provincial or local regulatory agency, department, bureau, commission, council or other governmental entity having jurisdiction over the manufacture, use, storage, import, transport, marketing, and sale (including packaging and labeling) of a Licensed Product in the Territory.

“**Sublicense Agreement**” means any agreement or arrangement pursuant to which Licensee (or an Affiliate or Sublicensee) grants to any third party any license rights of Licensee under the Agreement.

“**Sublicense Fee**” means the fee specified in Section 3.1(d) of the Patent License Agreement.

“**Sublicensee**” means any entity to whom an express sublicense has been granted under the Patent Rights.

“**Territory**” means the territory so indicated as the Territory in Section 1 of the Patent License Agreement.

“**Valid Claim**” means a claim of (i) an issued and unexpired patent included within the Patent Rights unless the claim has been held unenforceable or invalid by the final, un-reversed, and un-appealable decision of a court or other government body of competent jurisdiction, has been irretrievably abandoned or disclaimed, or has otherwise been finally admitted or determined to be invalid, un-patentable or unenforceable, whether through reissue, reexamination, disclaimer or otherwise, or (ii) a pending patent application within the Patent Rights to the extent the claim continues to be prosecuted in good faith provided that if a particular claim has not issued within five (5) years of its initial non-provisional, national-stage filing, it shall not be considered a Valid Claim for purposes of this Agreement unless and until such claim is included in an issued patent and qualifies under subsection (i) of this definition.

## 2. **License Grant and Commercialization**

### 2.1 Grant

- (a) Licensor grants to Licensee a royalty-bearing exclusive license (with the right to sublicense as set forth in Section 2.3) under Patent Rights for the Field and in the Territory to make, have made, distribute, have distributed,

use, offer for sale, sell, lease, loan, export and/or import Licensed Products.

- (b) This grant is subject to any rights of, or obligations to, the Government as set forth in Section 11.2 (Government Rights). Subject to Licensor's confidentiality obligations under Article 8, Licensor retains the right to practice the Patent Rights for its non-commercial teaching, research, education, and other educationally-related purposes, including the right to (i) publish the scientific findings from such research and (ii) grant third party not-for-profit institutions rights under the Patent Rights solely for non-commercial teaching, research, education, and other educationally-related purposes. In the event Licensor's Office of Technology Commercialization ("OTC") becomes aware of any proposed publication, including without limitation by George Georgiou, any researcher working with George Georgiou, or otherwise, that the OTC understands is likely to include the Licensed Products, then OTC agrees to use reasonable efforts to submit said publication for review by Licensee in advance of publication and to give due consideration to any responsive comments by Licensee. Said draft publication shall be treated as Licensor's Confidential Information pursuant to Section 8 hereof.
- (c) Licensor reserves all rights not expressly granted in the Agreement and disclaims the grant of any implied rights to Licensee.

## 2.2 Affiliates

Licensee may extend the license granted herein to any Affiliate provided that the Affiliate agrees in writing to be bound by the Agreement to the same extent as Licensee. Licensee agrees to deliver such written agreement to Licensor within thirty (30) calendar days following execution. No additional consideration above the consideration defined in this Patent License Agreement shall be due to Licensor in connection with such extension.

## 2.3 Sublicensing

Licensee and its Affiliates have the right to grant Sublicense Agreements under the Patent Rights. Each such Sublicense Agreement must be consistent with the terms of the Agreement, subject to the following:

- (a) Each Sublicensee shall be a party to a Sublicense Agreement that is consistent with, no less protective of Licensor's rights than, and does not conflict with, the terms of this Agreement, and shall include terms and conditions reasonably sufficient to enable Licensee to comply with the terms of this Agreement, including Sublicensor's right to terminate such Sublicense Agreement if Sublicensee challenges the validity of any Patent Rights in any legal proceeding. Each Sublicense Agreement shall be granted for material consideration. In the event of termination of the

Agreement, continued sublicense rights shall be governed by Section 7.5(a) (Effect of Termination). Sublicensees shall have the unlimited right to grant further sublicenses under any sublicense granted by the Licensee or its Affiliates pursuant to this Agreement, provided that (i) a sublicensee of such Sublicensee shall not have the right to grant further sublicenses without the prior written consent of Licensor, which consent shall not be unreasonably withheld or delayed, (ii) any sub-sublicense complies with the terms of this section, and (iii) such sub-sublicense is granted only to the extent it is necessary for commercialization of Licensed Products.

- (b) Licensor shall be given a true, complete, and correct copy of each Sublicense Agreement granted by Licensee or an Affiliate, and any modification or termination thereof, within thirty (30) days following the applicable execution of the respective Sublicense Agreement or any amendment to such Sublicense Agreement, and notwithstanding anything to the contrary herein, such Sublicense Agreement shall be deemed Licensee's Confidential Information. If the Sublicense Agreement is not in English, Licensee shall provide Licensor an accurate English translation of the sublicense. Licensee may redact portions of the Sublicense Agreement which constitute sensitive confidential information, as long as such information is not necessary to calculate or verify amounts owed to Licensor under this Patent License Agreement. Licensee will use good faith efforts to obtain the right to disclose to Licensor copies of any sub-sublicense agreements in a manner consistent with the provisions of this Section 2.3(b).
- (c) Notwithstanding any such Sublicense Agreement, Licensee will remain primarily liable to Licensor for all of the Licensee's duties and obligations contained in the Agreement, including without limitation the payment of running royalties due under Section 3.2.

#### 2.4 Diligent Commercialization

Licensee by itself, or through its Affiliates and Sublicensees, will use Commercially Reasonable Efforts to research, develop and commercialize at least one Licensed Product in the Field in the Territory. Without limiting the foregoing, Licensee will fulfill the Diligence Milestones specified in Section 2.4 of the Patent License Agreement by the deadlines indicated therein and (c) use diligent and Commercially Reasonable Efforts to perform and complete the plans described in the annual report submitted pursuant to Section 4.2 (Annual Written Progress Report). Licensor hereby agrees that the efforts of Sublicensees, Affiliates, and any third party contractors shall be deemed the acts of Licensee for purposes of satisfying this Section 2.4, and for the purposes of fees due under Section 3.1(b) of the Patent License Agreement.

### 3. Compensation

In consideration of rights granted to Licensee, Licensee will pay Licensor the following fees and royalties. All fees and royalties are not refundable and are not creditable against other fees and royalties. Each payment will reference the Patent License Agreement number and will be sent to Licensor's payment and accounting contact in Section 18 (Notices) of the Patent License Agreement.

#### 3.1 Non-Royalty Payments due from Licensee

- (a) *Patent Expenses.* Licensee will reimburse Licensor for the past patent expenses stated in Section 3.1(a) of the Patent License Agreement within thirty (30) days after the Effective Date. The stated amount is the current estimate for past patent expenses based on invoices received by the Licensor through the stated date. Licensee's obligations to pay all past and future patent expenses pursuant to Section 6 (Patent Expenses and Prosecution) will not be limited by such amount.

*Milestone Fees.* Licensee will pay Milestone Fees indicated in Section 3.1(b) of the Patent License Agreement by the Quarterly Payment Deadline for the Contract Quarter in which the Milestone Events set forth in Section 3.1(b) of the Patent License Agreement are achieved. Notwithstanding anything to the contrary, each Milestone Fee is payable only once under this Agreement, with respect to the initial accomplishment thereof, regardless of the number of Licensed Products (or indications therefor) or the number of times such Milestone Event may be achieved. [\*]

**\*Confidential Treatment Requested.**

- (c) *Scheduled License Fees.* Licensee will pay license fees in the amounts set forth in Sections 3.1(c) of the Patent License Agreement. Licensor will invoice Licensee for such fees in accordance with the stated schedule (i.e., thirty (30) days prior to the due date). Such invoices will be due and payable within thirty (30) days from the date of invoice.
- (d) *Sublicense Fees.* Licensee will pay Sublicense Fees indicated in Section 3.1(d) of the Patent License Agreement on or before the Quarterly Payment Deadline for the Contract Quarter.
- (e) *Assignment Fee.* In the event Licensee assigns this Patent License Agreement to a third party that is not an Affiliate of Licensee, or if Licensee assigns this Patent License Agreement in connection with a Change of Control, Licensee will pay the Assignment Fee forth in Section 3.1(e) of this Agreement within fifteen (15) days of the effective date of such assignment. Assignment Fee shall not be due for an assignment of this Patent License Agreement to an Affiliate of Licensee that is not made in connection with a Change of Control; provided, however, that if such Affiliate ceases to be an Affiliate of Licensee, then an Assignment Fee

shall become due and payable to Licensor within fifteen (15) days after such Affiliate ceases to be an Affiliate of Licensee. Assignments are further governed by Section 15 below.

### 3.2 Royalties

Licensee will pay a running royalty at the rate set forth in Section 3.2 of the Patent License Agreement [\*], payable on or before the Quarterly Payment Deadline for such Contract Quarter, subject to the following:

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- (b) No more than one royalty shall be paid to Licensor hereunder with respect to the sale of any one unit of Licensed Product, whether or not more than one patent or Valid Claim is applicable to the Licensed Product, or the development, manufacture, or performance thereof.
- (c) If Licensee, an Affiliate, or a Sublicensee reasonably determines that it is necessary or advisable to obtain a license to any patent(s) or patent application(s) owned, licensed, or controlled by a third party in any country of the Territory, then Licensee shall be entitled to deduct [\*] of the consideration paid to any such third party for any such rights in a particular country (such consideration, "Third Party Royalties") from any payments due Licensor under Section 3.2(a) of this Agreement for Net Product Sales in that particular country, provided that such amounts payable shall not be reduced, with respect to any Contract Quarter below [\*] of the amounts otherwise due Licensor with respect to such Contract Quarter for said Net Product Sales without such offset (with any amount of any such consideration not used to reduce payments due Licensor hereunder as a result of such limit remaining available for deduction from amounts due Licensor in future Contract Quarter for Net Product Sales in that particular country, subject to such [\*] limit in each Contract Quarter) Licensee, Affiliate, or Sublicensee reasonably determines that it is necessary or advisable to obtain a license to any patent(s) or patent application(s) owned, licensed, or controlled by a Third Party
- (d) Should a compulsory license be granted, or be the subject of a possible grant, to a third party under the applicable laws, rules, regulations, guidelines, or other directives of any Government in the Territory under the Patent Rights, the Party receiving notice thereof or otherwise becoming aware thereof shall promptly notify the other Party thereof, including any material information concerning such compulsory license, and the total amount payable under Section 3.2(a) with respect to sales of Licensed Products in such country will be adjusted to match any lower amount such third party may be allowed to pay with respect to the sales of such Licensed Products in such country, with such lower amount subject to further adjustments pursuant to Sections 3.2(c) above.

- (e) Subject to any earlier termination of this Agreement, amounts due under Section 3.2(a) shall only be payable on a country-by-country and Licensed Product-by-Licensed Product basis for Licensed Products that are made or sold in a particular country prior to the first date on which there are no Valid Claims of any Patent Right Covering such Licensed Product in such country, (such period for a particular Licensed Product in a particular country, the “Royalty Term” for such Licensed Product in such country) .

### 3.3 Non-cash Consideration

If Licensee receives or anticipates receipt of non-cash consideration from sales of Licensed Products or Sublicense Agreements, the manner in which Licensor will receive its compensation under the Agreement with respect to such non-cash consideration will be negotiated in good faith and timely agreed to by the Parties.

## 4. **Reports and Plans**

The reports specified in this Section 4 will be sent to Licensor’s payment and reporting contact identified in Section 18 (Notices) of the Patent License Agreement. Any special formatting requirements for such reports shall be mutually agreed upon in writing by Licensor and Licensee.

### 4.1 Quarterly Payment and Milestone Reports

On or before each Quarterly Payment Deadline, Licensee will deliver to Licensor a true and accurate report, certified by an officer of Licensee, giving such particulars of the business conducted by Licensee, its Affiliates and its Sublicensees (including copies of reports provided by Sublicensees and Affiliates to Licensee) during the preceding Contract Quarter under the Agreement as necessary for Licensor to account for Licensee’s payments hereunder, even if no payments are due. The reports shall continue to be delivered after the termination or expiration of the Agreement until such time as all Licensed Products permitted to be sold after termination or expiration have been sold or destroyed. Licensee shall provide information in sufficient detail to enable the royalties payable hereunder to be determined and to calculate all of the amounts payable under the Agreement. The report shall include:

- (a) The name of the Licensee, the Patent License Agreement number, and the period covered by the report;
- (b) The name of any Affiliates and Sublicensees whose activities are also covered by the report;
- (c) Identification of each Licensed Product for which any royalty payments have become payable;
- (d) Net Product Sales segregated on a product-by-product basis, and a country-by-country basis, or an affirmative statement that no Sales were

made. The report shall also itemize the permitted deductions from the gross revenue used to arrive at the resulting Net Product Sales on a product-by-product basis;

- (e) The applicable royalty rate;
- (f) An affirmative statement of whether any milestones with deadlines in that Contract Quarter under Section 2.4 and any milestones under Section 3.1(b) were met or not, and the resulting Milestone Fee payable;
- (g) Non-Royalty Sublicensing Consideration received by Licensee segregated on a Sublicense Agreement - by-Sublicense Agreement basis, or an affirmative statement that none was received;
- (h) If any consideration was received in currencies other than U.S. dollars, the report shall describe the currency exchange calculations; and
- (i) Any changes in accounting methodologies used to account for and calculate the items included in the report since the previous report.

#### 4.2 Annual Written Progress Report and Commercialization Plan

Within forty-five (45) days following the end of each Contract Year until the year following the year in which the first commercial sale of a Licensed Product occurred, Licensee will deliver to Licensor a true and accurate written progress report and commercialization plan, certified by an officer of Licensee, that summarizes (i) Licensee's efforts and accomplishments during the Contract Year to diligently commercialize Licensed Products, and (ii) Licensee's development and commercialization plans with respect to Licensed Products for the next Contract Year. The report shall also cover such activities by Affiliates and Sublicensees. The report shall contain the following information to the extent relevant to the activities under the Agreement:

- (a) The name of the Licensee, the Patent License Agreement number, the names of any Affiliates and Sublicensees, and the products and services being developed and/or commercialized;
- (b) The progress toward completing and the plans for completing the applicable milestone events pursuant to Sections 2.4 and 3.1(b);
- (c) The research and development activities, including status and plans for obtaining any necessary governmental approvals, performed during the past year, and the plans for research and development activities for the next year; and
- (d) The marketing activities for the past year and planned for the next year, and Licensee's internal estimate for sales for the next year.

## 5. **Payment, Records, and Audits**

### 5.1 Payments

All amounts referred to in the Patent License Agreement are expressed in U.S. dollars without deductions for taxes, assessments, fees, or charges of any kind. Each payment will reference the agreement number set forth at the beginning of the Patent License Agreement. All payments to Licensor will be made in U.S. dollars by check or wire transfer (Licensee to pay all wire transfer fees) payable to the payee identified in Section 18 of the Patent License Agreement and sent to the payment and reporting contact in Section 18 (Notices) of the Patent License Agreement.

### 5.2 Sales Outside the U.S.

If any currency conversion shall be required in connection with the calculation of payments hereunder, such conversion shall be made using the rate used by Licensee for its financial reporting purposes in accordance with Generally Accepted Accounting Principles (or foreign equivalent) or, in the absence of such rate, using the average of the buying and selling exchange rate for conversion between the foreign currency and U.S. Dollars, for current transactions as reported in *The Wall Street Journal* on the last business days of the Contract Quarter to which such payment pertains. Licensee may not make any tax withholdings from payments to Licensor, but Licensor agrees to supply to Licensee, upon written request, appropriate evidence from appropriate U.S. governmental agencies showing that Licensor is a resident of the United States of America for purposes of the U.S. income tax laws and is tax-exempt under such income tax laws.

### 5.3 Late Payments

Undisputed amounts that are not paid when due will accrue a late charge from the due date until paid, at a rate equal to 1.0% per month (or the maximum allowed by law, if less).

### 5.4 Records

For a period of four years after the Contract Quarter to which the records pertain, Licensee agrees that it and its Affiliates and Sublicensees will each keep complete and accurate records of their Net Product Sales, Milestone Fees, and Non-Royalty Sublicensing Consideration in sufficient detail to enable such payments to be determined and audited.

### 5.5 Auditing

Licensee and its Affiliates will permit an independent certified public accountant designated by Licensor and approved in writing by Licensee (which approval shall not be unreasonably withheld or delayed), at Licensor's expense, to examine

books, ledgers, and records relating solely to amounts payable hereunder, during regular business hours, at Licensee's or its Affiliate's place of business, on at least thirty (30) days advance notice, to the extent necessary to verify any payment required under the Agreement. For each Sublicensee, Licensee shall obtain such audit rights for Licensor or itself. If Licensee obtains such audit rights for itself, it will promptly conduct an audit of the Sublicensee's records upon Licensor's request and at Licensor's expense, and Licensee will furnish to Licensor a copy of the findings from such audit. No more than one audit of Licensee, each Affiliate, and each Sublicensee shall be conducted under this Section 5.5 in any calendar year. If any amounts due Licensor have been underpaid, then Licensee shall immediately pay Licensor the amount of such underpayment plus accrued interest due in accordance with Section 5.3. If the amount of underpayment is equal to or greater than 5% of the total amount due for the records so examined, Licensee will pay the cost of such audit. Such audits may, if mutually agreed upon in writing by Licensor and Licensee, consist of a self-audit conducted by Licensee at Licensor's expense and certified in writing by an authorized officer of Licensee. If the amounts due Licensor have been overpaid, the balance of overpayment shall be credited toward the next payment of monies owed Licensor. All information examined pursuant to this Section 5.5 shall be deemed to be the Confidential Information of the Licensee.

## 6. **Patent Expenses and Prosecution**

### 6.1 Patent Expenses

Licensee shall reimburse Licensor for all past documented, out-of-pocket expenses incurred by Licensor for filing, prosecuting, enforcing, defending and maintaining Patent Rights and related patent searches through the Effective Date of the Agreement, including those identified in Section 3.1(a) of the Patent License Agreement, and all such future expenses incurred by Licensor, for so long as, and in such countries as the Agreement remains in effect. Licensee will reimburse such patent expenses, within thirty (30) days after Licensee's receipt of an invoice, with such payment being made either directly to Prosecution Counsel or to Licensor, as elected by Licensor in writing on or before the date of the applicable invoice. Patent expense payment delinquencies (whether owed directly to Prosecution Counsel or to Licensor) that are not in dispute in good faith will be considered a payment default under Section 7.3(a).

### 6.2 Direction of Prosecution

Licensor will apply for, prosecute, and maintain during the term of this Agreement, the Patent Rights in the United States and in the foreign countries listed in Schedule 6.2 hereto. Licensor will confer with Licensee to develop a strategy for the prosecution and maintenance of Patent Rights. Licensor will request that copies of all documents prepared by the Prosecution Counsel for submission to governmental patent offices be provided to Licensee for review and comment prior to filing, to the extent practicable under the circumstances.

Licensee will be given reasonable opportunities to advise Licensor in the filing, prosecution, and maintenance of Patent Rights. At Licensee's request, and reasonably in advance of any filing, fee, or other action deadlines, Licensee shall be provided with copies of all prosecution documents relating to Patent Rights so that Licensee may have the opportunity to offer comments and remarks thereon, such comments and remarks to be given due consideration by Licensor. At its discretion, Licensor may allow Licensee to instruct Prosecution Counsel directly, provided, that (a) Licensor will maintain final authority in all decisions regarding the prosecution and maintenance of the Patent Rights, (b) Licensor may revoke this authorization to instruct Prosecution Counsel directly at any time, and (c) the Prosecution Counsel remains counsel to the Licensor with an appropriate contract (and shall not jointly represent Licensee unless requested by Licensee and approved by Licensor, and an appropriate engagement letter and conflict waiver are in effect). If Licensee wishes to instruct Prosecution Counsel directly or change Prosecution Counsel, Licensee may request to do so by following the Licensor's procedures for such. Licensor reserves in its sole discretion the ability to change Prosecution Counsel and to approve or disapprove any requested changes by Licensee. The Parties agree that they share a common legal interest to get valid enforceable patents and that Licensee will maintain as privileged all information received pursuant to this Section.

### 6.3 Ownership

All patent applications and patents will be in the name of Licensor (and any co-owner identified in Section 1 of the Patent License Agreement) and owned by Licensor (and such co-owner, if any). No payments due under the Patent License Agreement will be reduced solely as the result of co-ownership interests in the Patent Rights by Licensee or any other party.

### 6.4 Additional Foreign Filings

If Licensee wishes to pursue patent protection in countries other than the U.S., and the foreign countries listed in Schedule 6.2 hereto, then (i) Licensee shall notify Licensor in writing, subject to applicable bar dates, of such foreign countries in sufficient time to reasonably enable the preparation of such additional filings, (ii) Licensor will apply for, prosecute, and maintain during the term of this Agreement, the Patent Rights in such foreign countries, and (iii) Schedule 6.2 shall be automatically amended to include such foreign countries. If Licensee notifies Licensor in writing that it does not choose to pursue patent rights in a particular foreign country and Licensor chooses to do so, Licensor shall so notify Licensee and thereafter said patent application or patent shall no longer be included in the Patent Rights and Licensee shall have no further rights thereto.

### 6.5 Withdrawal from Paying Patent Costs

If at any time Licensee wishes to cease paying for any costs for a particular Patent Right or for patent prosecution in a particular jurisdiction, Licensee must give

Licensors at least ninety (90) days prior written notice and Licensee will continue to be obligated to pay for the patent costs which reasonably accrue during said notice period. Thereafter, said patent application or patent shall no longer be included in the Patent Rights and Licensee shall have no further rights thereto.

#### 6.6 U.S. Patent and Trademark Office Entity Size Status

Licensee represents that as of the Effective Date the entity size status of Licensee in accordance with the regulations of the U.S. Patent and Trademark Office is as set forth in Section 1 of the Patent License Agreement. Licensee will inform Licensor in writing on a timely basis of any change in its U.S. Patent and Trademark Office entity size status.

### 7. **Term and Termination**

#### 7.1 Term

Unless earlier terminated as provided herein, the term of the Agreement will commence on the Effective Date and continue on a country-by-country and Licensed Product-by-Licensed Product basis, until the expiration of the Royalty Term for a particular Licensed Product in a particular country (with the entire Agreement expiring on the expiration of the last-to-expire Royalty Term).

#### 7.2 Termination by Licensee

Licensee, at its option, may terminate the Agreement by providing Licensor written notice of intent to terminate, which such termination effective will be ninety (90) days following receipt of such notice by Licensor.

#### 7.3 Termination by Licensor

Licensor, at its option, may immediately terminate the Agreement, or any part of Patent Rights, or any part of Field, or any part of Territory, or the exclusive nature of the license grant, upon delivery of written notice to Licensee of Licensor's decision to terminate, if any of the following occur:

- (a) Licensee becomes in arrears in any payments due under the Agreement, and Licensee fails to make the required payment within thirty (30) days after delivery of written notice from Licensor; or
- (b) Licensee is in breach of any non-payment provision of the Agreement, and does not cure such breach within sixty (60) days after delivery of written notice from Licensor; or

Licensor delivers notice to Licensee of [\*], even in the event that Licensee cures such breaches in the allowed period, but only if [\*]; or

**\*Confidential Treatment Requested.**

- (d) Licensee or its Affiliate or Sublicensee participates in any proceeding or action to challenge the validity, enforceability, or scope of one or more of the Patent Rights. Provided however, this section shall not be applicable in the context of a Sublicensee or Affiliate defending against a patent infringement suit initiated by licensor, or if Licensee terminates a Sublicensee (in the event Sublicensee sues Licensor) within 30 days of receiving notice from Licensor that they are being sued by the Sublicensee.

#### 7.4 Other Conditions of Termination

The Agreement will terminate:

- (a) Immediately without the necessity of any action being taken by Licensor or Licensee, (i) if Licensee files for bankruptcy under Chapter 7 or Chapter 11 of the U.S. Bankruptcy Act or becomes insolvent, or (ii) Licensee's Board of Directors elects to liquidate its assets or dissolve its business, or (iii) Licensee makes an assignment for the benefit of creditors or (iv) if the business or assets of Licensee are otherwise placed in the hands of a receiver, assignee for the protection of creditors or trustee, whether by voluntary act of Licensee or otherwise; or
- (b) At any time by mutual written agreement between Licensee and Licensor.

#### 7.5 Effect of Termination

If the Agreement is terminated for any reason:

- (a) If a Sublicensee is in good standing under its Sublicense Agreement without any uncured defaults that would otherwise have entitled the Licensee to terminate such Sublicense Agreement, the Sublicensee may request Licensor to grant a direct license to the Sublicensee on comparable terms; which request must be in writing and received by Licensor not later than thirty (30) days after any termination of the Agreement. If Licensor determines that the Sublicensee is well qualified to continue as a direct licensee, Licensor will not unreasonably withhold consent for such request; in which event, said Sublicensee and Licensor will enter into a new mutually approved written license agreement that endeavors to preserve the essential benefits for each party that they enjoyed under the prior Agreement and Sublicense Agreement. For the avoidance of doubt, during the period between the termination of the Agreement and the date on which such a mutually approved written license agreement is consummated between the Sublicensee and Licensor, the Sublicense Agreement shall be deemed to continue with the Licensor directly. If no such mutually approved written license agreement is consummated between the Sublicensee and Licensor, the Sublicense Agreement shall be deemed to be terminated.

- (b) Licensee shall cease making, having made, distributing, having distributed, using, selling, offering to sell, leasing, loaning and importing any Licensed Products by the effective date of termination; and
- (c) Licensee shall tender payment of all accrued royalties and other accrued payments due to Licensor in accordance with the payment terms hereof; and
- (d) Nothing in the Agreement will be construed to release either Party from any obligation that matured prior to the effective date of termination; and
- (e) The provisions of Sections 8 (Confidentiality), 9 (Infringement and Litigation), 11 (Representations and Disclaimers), 12 (Limit of Liability), 13 (Indemnification), 14 (Insurance), 17 (Use of Name), 18 (Notices), and 19 (General Provisions) will survive any termination or expiration of the Agreement. In addition, the provisions of Sections 3 (Compensation), 4.1 (Quarterly Payment and Milestone Reports), 5 (Payment, Records and Audits), and 6.1 (Patent Expenses) shall survive with respect to all activities and payment obligations accruing prior to the termination or expiration of the Agreement.

## 8. Confidentiality

### 8.1 Definition

“Confidential Information” means all information that is of a confidential or proprietary nature to Licensor or Licensee and provided by one Party to the other Party under the Agreement.

### 8.2 Protection and Marking

Licensor and Licensee each agree that all Confidential Information disclosed in tangible form, and marked “confidential” and forwarded to one by the other, or if disclosed orally, is designated as confidential at the time of disclosure: (i) is to be held in strict confidence by the receiving Party, (ii) is to be used by and under authority of the receiving Party only as authorized in the Agreement, and (iii) shall not be disclosed by the receiving Party, its agents or employees without the prior written consent of the disclosing Party or as authorized in the Agreement. Licensee has the right to use and disclose Confidential Information of Licensor reasonably in connection with the exercise of its rights under the Agreement, including without limitation disclosing to Affiliates, Sublicensees, potential investors, acquirers, and others on a need to know basis, if such Confidential Information is provided under conditions which reasonably protect the confidentiality thereof. Each Party’s obligation of confidence hereunder includes, without limitation, using at least the same degree of care with the disclosing Party’s Confidential Information as it uses to protect its own Confidential Information, but always at least a reasonable degree of care.

### 8.3 Confidentiality of Terms of Agreement

Each Party agrees not to disclose to any third party the terms of the Agreement without the prior written consent of the other Party hereto, except each Party may disclose the terms of the Agreement: (a) to advisors, actual or potential Sublicensees, acquirers or investors, and others on a need to know basis, in each case, under appropriate confidentiality obligations substantially similar to those of this Section 8; and (b) to the extent necessary to comply with applicable laws and court orders (including, without limitation, The Texas Public Information Act, as may be amended from time to time, other open records laws, decisions and rulings, and securities laws, regulations and guidance). Notwithstanding the foregoing, the existence of the Agreement shall not be considered Confidential Information.

### 8.4 Disclosure Required by Court Order or Law

If the receiving Party is required to disclose Confidential Information of another Party hereto, or any terms of the Agreement, pursuant to the order or requirement of a court, administrative agency, or other governmental body or applicable law, the receiving Party may disclose such Confidential Information or terms to the extent required, provided that the receiving Party shall use reasonable efforts to provide the disclosing Party with reasonable advance notice thereof to enable the disclosing Party to seek a protective order and otherwise seek to prevent such disclosure. To the extent that Confidential Information so disclosed does not become part of the public domain by virtue of such disclosure, it shall remain Confidential Information protected pursuant to Section 8.

### 8.5 Copies

Each Party agrees not to copy or record any of the Confidential Information of the other Party, except as reasonably necessary to exercise its rights or perform its obligations under the Agreement, and for archival and legal purposes.

### 8.6 Continuing Obligations

Subject to the exclusions listed in Section 8.7, the Parties' confidentiality obligations under the Agreement will survive termination of the Agreement and will continue for a period of five (5) years thereafter.

### 8.7 Exclusions

Information shall not be considered Confidential Information of a disclosing Party under the Agreement to the extent that the receiving Party can establish by competent written proof that such information:

- (a) Was in the public domain at the time of disclosure; or

- (b) Later became part of the public domain through no act or omission of the recipient Party, its employees, agents, successors or assigns in breach of the Agreement; or
- (c) Was lawfully disclosed to the recipient Party by a third party having the right to disclose it not under an obligation of confidentiality; or
- (d) Was already known by the recipient Party at the time of disclosure; or
- (e) Was independently developed by the recipient Party without use of ‘ the disclosing Party’s Confidential Information.

#### 8.8 Copyright Notice

The placement of a copyright notice on any Confidential Information will not be construed to mean that such information has been published and will not release the other Party from its obligation of confidentiality hereunder.

### 9. **Infringement and Litigation**

#### 9.1 Notification

If either Licensor’s designated office for technology commercialization or Licensee becomes aware of any alleged, potential or actual infringement of Patent Rights, each Party shall promptly notify the other of such in writing. Within two (2) business days of such notification (the “SRA Notice Period”), Licensor agrees to notify Licensee in writing if the infringing party is a party to a sponsored research agreement with the Licensor [\*].

**\*Confidential Treatment Requested.**

#### 9.2 Licensee’s Enforcement Rights

With respect to any potential infringement of the Patent Rights, Licensee shall have the first and primary right, but not the obligation, to, at its expense, initiate, prosecute, and control any action or legal proceedings, and/or enter into a settlement, including any declaratory judgment action, with respect thereto. In the event Licensor provides Licensee with an SRA Notice during the SRA Notice Period, Licensee shall not file an infringement lawsuit against the third party identified in such SRA Notice for at least [\*] from the date of such SRA Notice. In any such litigation brought by Licensee, Licensee shall have the right to use and sue in Licensor’s name and join Licensor as a party to such litigation only with the prior written consent of Licensor, and Licensor shall cooperate reasonably with respect thereto, as requested and at the expense of Licensee. If, within one hundred eighty (180) calendar days of the notice in Section 9.1, Licensee has neither brought, nor is Licensee diligently prosecuting an infringement or other action with respect to such potential infringement, then Licensor shall have the right, at its expense, to bring suit to enforce such Patent Rights against such potential infringer, at its own expense, unless Licensee has provided Licensor with a reasonable strategic rationale for not taking action to

terminate such potential infringement. Notwithstanding the foregoing, Licensor shall not, and shall not permit any third party to, proceed against an alleged infringer of the Patent Rights in the Territory (1) unless significant damages are reasonably expected to be recovered from the infringer in such proceeding and (2) without first consulting with Licensee regarding the strategy for such proceeding and considering in good faith Licensee's comments regarding such proceeding.

### 9.3 Litigation Control

The Party pursuing or controlling any action or defense under Section 9.2 (the "Controlling Party") shall be free to enter into a settlement, consent judgment, or other voluntary disposition of any such action or defense, provided, however, that (i) the Controlling Party shall consult with the other Party (the "Secondary Party") prior to entering into any settlement or voluntary disposition thereof, (ii) any settlement, consent judgment or other voluntary disposition of such actions which (1) subjects the Secondary Party to any non-indemnified liability or obligation or (2) admits fault or wrongdoing on the part of Secondary Party must, in each case, be approved in advance and in writing by the Secondary Party, (iii) any settlement, consent judgment or other voluntary disposition of such actions which materially limits the scope, validity, or enforceability of, or otherwise may adversely affect, any Patent Rights shall not be entered into, consented to, approved, or agreed upon without the other Party's prior written approval, and (iv) any settlement, consent judgment or other voluntary disposition of such actions that would reasonably be expected to materially adversely affect the Patent Rights or the ability of Licensee to manufacture, use, market or sell Licensed Products shall not be entered into, consented to, approved, or agreed upon without Licensee's prior written consent. With respect to clause (ii) or (iii) above in this Section 9.3, the Secondary Party shall provide the Controlling Party notice of its approval or denial of such approval within [\*] business days of any request for such approval by the Controlling Party, provided that (X) in the event Secondary Party wishes to deny such approval, such notice shall include a written description summarizing the Secondary Party's reasonable objections to the proposed settlement, consent judgment, or other voluntary disposition and (Y) Secondary Party shall be deemed to have approved such proposed settlement, consent judgment, or other voluntary disposition in the event it fails to provide such notice within such [\*] business day period.

**\*Confidential Treatment Requested.**

### 9.4 Sharing Net Recovery

Any recovery or damages received by the Controlling Party with respect to the infringement of the rights to the Patent Rights granted under this Agreement, or in settlement of any matter subject to Section 9.2 shall (i) first be used to reimburse the Parties pro rata for unreimbursed reasonable, documented litigation expenses (excluding, with respect to any costs or expenses incurred by Licensor, compensation of any employees or consultants of Licensor or any Affiliate thereof) incurred in connection with such action or settlement, and the remainder shall be split [\*] to Controlling Party and [\*] to Secondary Party. Notwithstanding

the foregoing, the Secondary Party, at its expense, shall have the right to be represented by counsel of its choice in any proceeding governed by this Section.

**\*Confidential Treatment Requested.**

10. **Export Compliance**

Licensee understands that the Arms Export Control Act (AECA), including its implementing International Traffic In Arms Regulations (ITAR), and the Export Administration Act (EAA), including its Export Administration Regulations (EAR), are some (but not all) of the laws and regulations that comprise the U.S. export laws and regulations. Licensee further understands that the U.S. export laws and regulations include (but are not limited to): (a) ITAR and EAR product/service/data-specific requirements; (b) ITAR and EAR ultimate destination-specific requirements; (c) ITAR and EAR end user-specific requirements; (d) Foreign Corrupt Practices Act; and (e) anti-boycott laws and regulations. Licensee will comply with all then-current applicable export laws and regulations of the U.S. Government (and other applicable U.S. laws and regulations) pertaining to the Licensed Products (including any associated products, items, articles, computer software, media, services, technical data, and other information). Licensee certifies that it will not, directly or indirectly, export (including any deemed export), nor re-export (including any deemed re-export) the Licensed Products (including any associated products, items, article's, computer software, media, services, technical data, and other information) in violation of applicable U.S. laws and regulations. Licensee will include a provision in its agreements, substantially similar to this Section 10, with its Sublicensees, third party wholesalers and distributors, and physicians, hospitals or other healthcare providers who purchase a Licensed Product, requiring that these parties comply with all then-current applicable U.S. export laws and regulations and other applicable U.S. laws and regulations.

11. **Representations and Disclaimers**

11.1 Licensor Representations

Except for the rights, if any, of the Government as set forth in Section 11.2, Licensor represents and warrants to Licensee that to the knowledge of Licensor's Office of Technology Commercialization (i) Licensor is the owner of the entire right, title, and interest in and to Patent Rights (other than the right, title and interest of any joint owner identified in Section 1 of the Patent License Agreement), (ii) Licensor has the right to grant licenses hereunder, (iii) Licensor has not knowingly granted and will not knowingly grant licenses or other rights under the Patent Rights that are in conflict with the terms and conditions in the Agreement, (iv) Licensor's execution and performance of this Agreement will not result in a breach of any other contract to which it is, or will become, a party, and (v) OTC has not received any written notification, alleging that the Patent Rights are invalid or unenforceable or that the exercise by Licensee of any rights granted hereunder will infringe on or constitute misappropriation of any patent or other proprietary right of any third party.

## 11.2 Government Rights

Licensee understands that Patent Rights may have been developed under a funding agreement with Government and, if so, that Government may have certain rights relative thereto. The Agreement is made subject to the Government's rights under any such agreement and under any applicable Government law or regulation. To the extent that there is a conflict between any such agreement, such applicable law or regulation and the Agreement, the terms of such Government agreement, and applicable law or regulation, shall prevail. Licensee agrees that, to the extent required by U.S. laws and regulations, Licensed Products used or sold in the U.S. will be manufactured substantially in the U.S., unless a written waiver is obtained in advance from the U.S. Government.

## 11.3 Licensor Disclaimers

EXCEPT AS SPECIFICALLY SET FORTH IN SECTION 11.1, LICENSEE UNDERSTANDS AND AGREES THAT LICENSOR MAKES NO REPRESENTATIONS OR WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING, WITHOUT LIMITATION, AS TO THE LICENSED PRODUCTS OR LICENSED SERVICES, OR AS TO THE OPERABILITY OR FITNESS FOR ANY USE OR PARTICULAR PURPOSE, MERCHANTABILITY, SAFETY, EFFICACY, APPROVABILITY BY REGULATORY AUTHORITIES, TIME AND COST OF DEVELOPMENT, PATENTABILITY, AND/OR BREADTH OF PATENT RIGHTS. LICENSOR MAKES NO REPRESENTATION AS TO WHETHER ANY PATENT WITHIN PATENT RIGHTS IS VALID, OR AS TO WHETHER THERE ARE ANY PATENTS NOW HELD, OR WHICH WILL BE HELD, BY OTHERS OR BY LICENSOR THAT MIGHT BE REQUIRED FOR USE OF PATENT RIGHTS IN FIELD. NOTHING IN THE AGREEMENT WILL BE CONSTRUED AS CONFERRING BY IMPLICATION, ESTOPPEL OR OTHERWISE ANY LICENSE OR RIGHTS TO ANY PATENTS OR TECHNOLOGY OF LICENSOR OTHER THAN THE PATENT RIGHTS, WHETHER SUCH PATENTS ARE DOMINANT OR SUBORDINATE TO THE PATENT RIGHTS. LICENSOR HAS NO OBLIGATION TO FURNISH TO LICENSEE ANY KNOW-HOW, TECHNOLOGY OR TECHNOLOGICAL INFORMATION.

## 11.4 Licensee Representation

By execution of the Agreement, Licensee represents, acknowledges, covenants and agrees (a) that Licensee has not been induced in any way by Licensor or its employees to enter into the Agreement, and (b) that Licensee has been given an opportunity to conduct sufficient due diligence with respect to all items and issues pertaining to this Section 11 (Representations and Disclaimers) and all other matters pertaining to the Agreement; and (c) that Licensee has adequate knowledge and expertise, or has utilized knowledgeable and expert consultants, to adequately conduct the due diligence, and (d) that Licensee accepts all risks

inherent herein. Licensee represents that it is a duly organized, validly existing entity of the form indicated in Section 1 of the Patent License Agreement, and is in good standing under the laws of its jurisdiction of organization as indicated in Section 1 of the Patent License Agreement, and has all necessary corporate or other appropriate power and authority to execute, deliver and perform its obligations hereunder.

12. **Limit of Liability**

IN NO EVENT SHALL LICENSOR, THE UNIVERSITY SYSTEM IT GOVERNS, ITS MEMBER INSTITUTIONS, INVENTORS, REGENTS, OFFICERS, EMPLOYEES, STUDENTS, AGENTS OR AFFILIATED ENTERPRISES (COLLECTIVELY, "LICENSOR COVERED PARTIES"), BE LIABLE FOR ANY INDIRECT, SPECIAL, CONSEQUENTIAL, INCIDENTAL, EXEMPLARY, OR PUNITIVE DAMAGES (INCLUDING, WITHOUT LIMITATION, DAMAGES FOR LOSS OF PROFITS OR REVENUE) ARISING OUT OF OR IN CONNECTION WITH THE AGREEMENT OR ITS SUBJECT MATTER, REGARDLESS OF WHETHER ANY SUCH PARTY KNOWS OR SHOULD KNOW OF THE POSSIBILITY OF SUCH DAMAGES.

OTHER THAN FOR CLAIMS AGAINST LICENSEE FOR INDEMNIFICATION PROVIDED UNDER SECTION 13 WITH RESPECT TO THIRD PARTY CLAIMS, IN NO EVENT SHALL LICENSEE, ITS AFFILIATES OR SUBLICENSEES BE LIABLE TO LICENSOR COVERED PARTIES FOR ANY INDIRECT, SPECIAL, INCIDENTAL, CONSEQUENTIAL, EXEMPLARY OR PUNITIVE DAMAGES (INCLUDING, WITHOUT LIMITATION, DAMAGES FOR LOSS OF PROFITS OR REVENUE) ARISING OUT OF OR IN CONNECTION WITH THE AGREEMENT OR ITS SUBJECT MATTER, REGARDLESS OF WHETHER LICENSEE KNOWS OR SHOULD HAVE KNOWN OF THE POSSIBILITY OF SUCH DAMAGES.

13. **Indemnification**

13.1 Indemnification Obligation

Subject to Section 13.2, Licensee agrees to hold harmless, defend and indemnify Licensor, the university system it governs, its member institutions, its Regents, officers, employees, students and agents (the "Indemnified Parties", or an "Indemnified Party") from and against any liabilities, damages, causes of action, suits, judgments, liens, penalties, fines, losses, costs and expenses (including, without limitation, reasonable attorneys' fees and other expenses of litigation) (collectively "Liabilities") resulting from claims or demands brought by third parties against an Indemnified Party on account of any injury or death of persons, damage to property, or any other damage or loss arising out of the exercise or practice by or under authority of Licensee, its Affiliates or their Sublicensees, or third party wholesalers or distributors, or physicians, hospitals or other healthcare providers who purchase a Licensed Product, of the rights granted hereunder.

13.2 Conditions of Indemnification

Licensee shall have no responsibility or obligation under Section 13.1 for any Liabilities to the extent caused by the gross negligence or willful misconduct by an Indemnified Party. Obligations to indemnify, and hold harmless under Section 13.1 are subject to: (a) to the extent authorized by the Texas Constitution and the laws of the State of Texas, and subject to the statutory duties of the Texas Attorney General, the Indemnified Party giving Licensee control of the defense and settlement of the claim and demand; and (b) to the extent authorized by the Texas Constitution and the laws of the State of Texas and subject to statutory duties of the Texas Attorney General, the Indemnified Party providing assistance reasonably requested by Licensee, at Licensee's expense.

14. **Insurance**

14.1 Insurance Requirements

Prior to any Licensed Product being used in humans or sold (including for the purpose of obtaining regulatory approvals), by Licensee, an Affiliate, or by a Sublicensee, and for a period of five years after the Agreement expires or is terminated, Licensee shall, at its sole cost and expense, procure and maintain commercial general liability insurance or an equivalent program of self-insurance in commercially reasonable and appropriate amounts for the Licensed Product being used or sold. Licensee shall use commercially reasonable efforts to have Licensor named as an additional insured party. Such commercial general liability insurance shall provide, without limitation: (i) product liability coverage; (ii) broad form contractual liability coverage for Licensee's indemnification under the Agreement; and (iii) coverage for litigation costs.

14.2 Evidence of Insurance and Notice of Changes

Upon request by Licensor, Licensee shall provide Licensor with written evidence of such insurance. Additionally, Licensee shall provide Licensor with written notice of at least 30 days prior to Licensee cancelling, not renewing, or materially changing such insurance.

15. **Assignment**

**\*Confidential Treatment Requested.**

The Agreement may not be assigned by Licensee without the prior written consent of Licensor, which consent will not be unreasonably withheld; provided, however, that Licensee shall be permitted to assign this Agreement to (i) any of its Affiliates, [\*]. A Change of Control shall be considered an assignment of the Agreement. For any permitted assignment to be effective, (a) the Licensee must be in good standing under this Agreement, (b) the assignment fee, if applicable, shall be payable as specified in Section 3.1(e) of the Agreement (c) the assignee must assume in writing all of Licensee's interests, rights, duties and obligations under the Agreement and agree to comply with all terms and conditions of the Agreement as if the assignee were an original Party to the Agreement and, (d) provide written notice to the Licensor of such assignment no less

than 15 days after completion of such assignment. Any such assignment must be of all rights and obligations of Licensee, such that there is only one existing Licensee at any one time.

16. **Governmental Markings**

16.1 Patent Markings

To the extent reasonably practical, Licensee agrees to mark, and shall use commercially reasonable efforts to ensure that its Affiliates, licensees, and sublicensees mark, all Licensed Products with the number of any applicable patent(s) licensed hereunder as part of the Patent Rights in accordance with each country's patent marking laws, including Title 35, U.S. Code, or if such marking is not practicable, shall so mark the accompanying outer box or product insert for Licensed Products accordingly.

16.2 Governmental Approvals and Marketing of Licensed Products

Licensee will be responsible for obtaining all necessary Governmental approvals for the development, production, distribution, sale, and use of any Licensed Product, at Licensee's expense, including, without limitation, any safety studies. Licensee will have sole responsibility for any warning labels, packaging and instructions as to the use and the quality control for any Licensed Product.

16.3 Foreign Registration and Laws

Licensee agrees to register the Agreement with any foreign governmental agency that requires such registration; and Licensee will pay all costs and legal fees in connection with such registration. Licensee is responsible for compliance with all foreign laws affecting the Agreement or the Sale of Licensed Products to the extent there is no conflict with United States law, in which case United States law will control.

17. **Use of Name**

Licensee will not use the name, trademarks or other marks of Licensor (or the name of the university system it governs, its member institutions, any of its Regents or employees) without the advance written consent of Licensor; provided however, in connection with describing the Agreement to existing and prospective investors and Sublicensees, Licensee may identify Licensor's name as the licensor. Licensor may use Licensee's name and logo for annual reports, brochures, website, and internal reports without prior consent.

18. **Notices**

Any notice or other communication of the Parties required or permitted to be given or made under the Agreement will be in writing and will be deemed effective when sent in a manner that provides confirmation or acknowledgement of delivery and received at the

address set forth in Section 18 of the Patent License Agreement (or as changed by written notice pursuant to this Section 18). Notices required under the Agreement may be delivered via E-mail provided such notice is confirmed in writing as indicated.

Notices shall be provided to each Party as specified in the "Contact for Notice" address set forth in Section 18 of the Patent License Agreement. Each Party shall update the other Party in writing with any changes in such contact information.

19.

## **General Provisions**

### 19.1 Binding Effect

The Agreement is binding upon and inures to the benefit of the Parties hereto, their respective executors, administrators, heirs, permitted assigns, and permitted successors in interest.

### 19.2 Construction of Agreement

Headings are included for convenience only and will not be used to construe the Agreement. The Parties acknowledge and agree that both Parties substantially participated in negotiating the provisions of the Agreement; therefore, both Parties agree that any ambiguity in the Agreement shall not be construed more favorably toward one Party than the other Party, regardless of which Party primarily drafted the Agreement.

### 19.3 Counterparts and Signatures

The Agreement may be executed in multiple counterparts, each of which shall be deemed an original, but all of which taken together shall constitute one and the same instrument. A Party may evidence its execution and delivery of the Agreement by transmission of a signed copy of the Agreement via facsimile or email.

### 19.4 Compliance with Laws

Licensee will comply with all applicable federal, state and local laws and regulations, including, without limitation, all export laws and regulations.

### 19.5 Governing Law

The Agreement will be construed and enforced in accordance with laws of the U.S. and the State of Texas, without regard to choice of law and conflicts of law principles.

19.6 Modification

Any modification of the Agreement will be effective only if it is in writing and signed by duly authorized representatives of both Parties. No modification will be made by email communications.

19.7 Severability

If any provision hereof is held to be invalid, illegal or unenforceable in any jurisdiction, the Parties hereto shall negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties, and all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such other provisions in any other jurisdiction, so long as the essential essence of the Agreement remains enforceable.

19.8 Third Party Beneficiaries

Nothing in the Agreement, express or implied, is intended to confer any benefits, rights or remedies on any entity, other than the Parties and their permitted successors and assigns. However, if there is a joint owner of any Patent Rights identified in Section 1 of the Patent License Agreement (other than Licensee), then Licensee hereby agrees that the following provisions of these Terms and Conditions extend to the benefit of the co-owner identified therein (excluding the Licensee to the extent it is a co-owner) as if such co-owner was identified in each reference to the Licensor but only if such co-owner is bound by all of Licensor's obligations under this Agreement: the retained rights under clause (b) of Section 2.1; Section 11.3 (Licensor Disclaimers); Section 12 (Limitation of Liability); Section 13 (Indemnification); Section 14.1 (Insurance Requirements); Section 17 (Use of Name); and Section 19.10 (Sovereign Immunity, if applicable).

19.9 Waiver

Neither Party will be deemed to have waived any of its rights under the Agreement unless the waiver is in writing and signed by such Party. No delay or omission of a Party in exercising or enforcing a right or remedy under the Agreement shall operate as a waiver thereof.

19.10 Sovereign Immunity

Nothing in the Agreement shall be deemed or treated as any waiver of Licensor's sovereign immunity.

19.11 Entire Agreement

The Agreement constitutes the entire Agreement between the Parties regarding the subject matter hereof, and supersedes all prior written or verbal agreements, representations and understandings relative to such matters.

19.12 Claims Against Licensor for Breach of Agreement

Licensee acknowledges that any claim for breach of the Agreement asserted by Licensee against Licensor shall be subject to Chapter 2260 of the Texas Government Code and that the process provided therein shall be Licensee's sole and exclusive process for seeking a remedy for any and all alleged breaches of the Agreement by Licensor or the State of Texas.

19.13 Grant of Security Interest

Licensee hereby grants to Licensor a security interest in and to Licensee's rights under the Patent License Agreement, as collateral security for the payment by Licensee of any and all sums which may be owed from time to time by Licensee to Licensor. Licensor shall have all rights of a secured party as specified in the Texas Uniform Commercial Code relative to this security interest and the enforcement thereof. Licensee hereby authorizes Licensor to file with the appropriate governmental agencies appropriate UCC-1 financing statements to evidence this security interest.

— END OF EXHIBIT A —

**Schedule 6.2**

**\*Confidential Treatment Requested.**

[\*]

Licensee: Aeglea BioTherapeutics, Inc.      CONFIDENTIAL Exclusive PLA  
The University of Texas at Austin      Schedule 6.2 Agreement No. PM1401501  
US 4915892v.1

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**Schedule 20.2**

<b>Docket No.</b>	<b>Title</b>	<b>Application No.</b>	<b>Registration No.</b>
AEG545/4-002US US	Compositions of Engineered Human Arginases and Methods for Treating Cancer	12/610,685	8,440,184
AEG545/4-002REUS US	Compositions of Engineered Human Arginases and Methods for Treating Cancer	14/711,916 (Reissue of 12/610685)	
AEG545/4-002CONUS US	Compositions of Engineered Human Arginases and Methods for Treating Cancer	13/863,448	9,050,340
AEG545/4-002CON2US US	Compositions of Engineered Human Arginases and Methods for Treating Cancer	14/275,259	
AEG545/4-002CON3US US	Compositions of Engineered Human Arginases and Methods for Treating Cancer	15/270,955	
AEG545/4-002CA Canada	Compositions of Engineered Human Arginases and Methods for Treating Cancer	2742497	
AEG545/4-002EP Europe	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002CH Switzerland	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002DE Germany	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1 (DE 6020090375 82.2)	2350273
AEG545/4-002DK Denmark	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002DIVEP Europe	Compositions of Engineered Human Arginases and Methods for Treating Cancer	16163214.6	
AEG545/4-002ES Spain	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002FR France	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002GB United Kingdom	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002HK Hong Kong (EP)	Compositions of Engineered Human Arginases and Methods for Treating Cancer	12100429.7	2350273
AEG545/4-002IE Ireland	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-00211 Italy	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002JP Japan	Compositions of Engineered Human Arginases and Methods for Treating Cancer	2011-534855	5695570
AEG545/4-002NL Netherlands	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002ND Norway	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002PL Poland	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002SE Sweden	Compositions of Engineered Human Arginases and Methods for Treating Cancer	09824219.1	2350273
AEG545/4-002TR Turkey	Compositions of Engineered Human Arginases and Methods for Treating Cancer	TR 2016/07968	2350273
AEG545/4-003US US	Methods for Purifying Pegylated Arginase	13/380,776	8,679,479
AEG545/4-004US US	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	13/020,268	8,709,407
AEG545/4-004DIVUS US	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	14/225,518	9,279,119

Licensee: Aeglea BioTherapeutics, Inc.      CONFIDENTIAL      Exclusive PLA  
The University of Texas at Austin      Schedule 20.2-1      Agreement No. PM1401501  
US 4915892v.1

<b>Docket No.</b>	<b>Title</b>	<b>Application No.</b>	<b>Registration No.</b>
AEG545/4-004DIV2US US	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	15/052,978	
AEG545/4-004AU Australia	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	2011212885	2011212885
AEG545/4-004CA Canada	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	2788689	
AEG545/4-004CN China	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	201180013307.X	
AEG545/4-004EP Europe	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	11740355.0	
AEG545/4-004HK Hong Kong (CN)	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	13106011.7	
AEG545/4-0041P Japan	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	2012-552084	5875990
AEG545/4-004KR Korea	Engineered Enzymes with Methionine-Gamma-Lyase Enzymes and Pharmacological Preparations Thereof	10-2012-7023176	

Licensee: Aeglea BioTherapeutics, Inc.  
The University of Texas at Austin  
US 4915892v.1

CONFIDENTIAL  
Schedule 20.2-2

Exclusive PLA  
Agreement No. PM1401501

## AMENDMENT #1 TO AMENDED AND RESTATED PATENT LICENSE AGREEMENT

This Amendment #1 to Amended and Restated Patent License Agreement (as defined below) is made and entered into as of the date of last signature below (“Amendment Effective Date”) by and between **Aeglea BioTherapeutics Inc.**, a Delaware corporation, with its principal place of business at 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746 (“**Licensee**”) and the **University of Texas at Austin**, on behalf of the Board of Regents of the University of Texas System, a not-for-profit organization and agency of the State of Texas, having its principal place of business at 2935 W. Braker Lane, Suite 1.9A (R3500), Austin, Texas 78759 (“**Licensor**”), each a “Party” and collectively, “Parties”.

### Background

A. Licensor and Licensee entered into an Amended and Restated Patent License Agreement (UTA No. PM1401501) with an Effective Date of January 31<sup>st</sup>, 2017 (“ARPLA”). Capitalized terms used herein without definition shall have meanings given to them in the ARPLA.

B. Licensor and Licensee wish to amend the ARPLA as set forth below in order to (i) add in Licensee’s business address and place of incorporation and (ii) update the list of Patent Rights;

NOW, THEREFORE, in consideration of the mutual covenants and promises herein contained, the Parties hereby agree as follows:

1. In Section 1 of the ARPLA, the name of Licensee shall be deleted in its entirety and replaced by the following: **Aeglea Biotherapeutics, Inc.**, a Delaware corporation, with its principal place of business at 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746.
2. In Section 1 of the ARPLA, the Patent Rights table should be deleted in its entirety and replaced with the following:

Patent Rights				
App. No./ Date of Filing	Title	Inventor(s)	Jointly Owned? (Y/N; if Y, with whom?)	Prosecution Counsel
US61/871,727 filed 8/29/2013	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
US61/948,106 filed 3/05/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC

Licensee: Aeglea BioTherapeutics, Inc. CONFIDENTIAL  
Exclusive PLA  
The University of Texas at Austin Page 1 Agreement No. PA1401502

**\*Confidential Treatment Requested.**

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US14/472,779 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
South Korea 10- 2016-7008299 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
PCT/US2014/0 53374 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
JP 2016-537886 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Israel 244263 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Europe 14839001.6 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
China 201480054224.9 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Canada 2,922,557 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Australia 2014312168 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
US 61/871,768 filed 8/29/2013	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei- Cheng Lu	No	Parker Highlander PLLC
US 14/472,750 Issued as 9,481,877 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei- Cheng Lu	No	Parker Highlander PLLC

Licensee: Aeglea BioTherapeutics, Inc.CONFIDENTIALEXclusive PLA  
The University of Texas at AustinPage 2Agreement No. PA1401502

**\*Confidential Treatment Requested.**

US 15/297,102 Issued as 9,624,484 filed 10/18/2016	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
US 15/451,349 filed 3/06/2017	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
South Korea 10-2016-7007045 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
PCT/US2014/053359 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
JP 2016-537882 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Israel 244261 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Europe 14841106.9 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
China 201480050681.0 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC

Licensee: Aeglea BioTherapeutics, Inc. CONFIDENTIAL Exclusive PLA  
The University of Texas at Austin Page 3 Agreement No. PA1401502

**\*Confidential Treatment Requested.**

Canada 2,922,550 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Australia 2014312159 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
[*]	[*]	[*]	[*]	[*]
[*]	[*]	[*]	[*]	[*]
[*]	[*]	[*]	[*]	[*]
[*]	[*]	[*]	[*]	[*]
[*]	[*]	[*]	[*]	[*]

**\*Confidential Treatment Requested.**

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IN WITNESS THEREOF, Licensor and Licensee have entered into this Amendment effective as of the Amendment Effective Date.

THE UNIVERSITY OF TEXAS AT AUSTIN ON BEHALF OF THE AEGLEA BIOTHERAPEUTICS, INC.  
BOARD OF REGENTS  
OF THE UNIVERSITY OF TEXAS SYSTEM

By: /s/ Daniel W. Sharp, J.D.  
Daniel W. Sharp, J.D.  
Associate Vice President for Research and Director, Office of Technology  
Commercialization

By: /s/ Anthony Quinn  
Anthony Quinn, Ph.D.  
CEO

Date: 8/4/17

Date: 10 August 2017

Licensee: Aeglea BioTherapeutics, Inc.      CONFIDENTIAL Exclusive PLA  
The University of Texas at Austin      Page 5      Agreement No. PA1401502

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**AMENDMENT #2 TO AMENDED AND RESTATED PATENT LICENSE AGREEMENT**

This Amendment #2 (the “Amendment”) to the Amended and Restated Patent License Agreement (as defined below) is made and entered into as of the date of last signature below (“Amendment Effective Date”) by and between **Aeglea BioTherapeutics, Inc.**, a Delaware corporation, with its principal place of business at 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746 (“Licensee”) and the **University of Texas at Austin**, on behalf of the Board of Regents of the University of Texas System, having its principal place of business at 2935 W. Braker Lane, Suite 1.9A (R3500), Austin, Texas 78759 (“Licensor”), each a “Party” and collectively, “Parties”.

**Background**

A. Licensor and Licensee entered into an Amended and Restated Patent License Agreement (UTA No. PM1401501) with an Effective Date of January 31, 2017, as amended by Amendment #1 (UTA No. PA1401502) effective as of August 10, 2017 (collectively, the “ARPLA”);

B. Licensor and Licensee wish to amend the ARPLA as set forth below in order to revise the diligence milestone deadlines;

NOW, THEREFORE, in consideration of the mutual covenants and promises herein contained, the Parties hereby agree as follows:

1. **Intent.** Except as expressly provided in this Amendment, the ARPLA will remain unchanged and in full force and effect in accordance with its original terms. Capitalized terms used herein without definition shall have meanings given to them in the ARPLA.
2. **Section 2.4.** Section 2.4 (Diligence Milestones table) of the ARPLA is hereby deleted and replaced with the following:

2.4	Diligence Milestones
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1

Licensee: Aeglea BioTherapeutics, Inc.  
The University of Texas at Austin

CONFIDENTIAL  
Agreement No. PM1401503

Amd. To ARPLA

**\*Confidential Treatment Requested.**

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IN WITNESS THEREOF, Licensor and Licensee have entered into this Amendment effective as of the Amendment Effective Date.

**THE UNIVERSITY OF TEXAS AT AUSTIN ON BEHALF OF THE AEGLEA BIOTHERAPEUTICS, INC.  
BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM**

/s/ Daniel W. Sharp, J.D.

Daniel W. Sharp, J.D.

Associate Vice President for Research and Director, Office of Technology  
Commercialization

/s/ Anthony Quinn

Anthony Quinn, M.B Ch.B, Ph.D., FRCP  
Interim Chief Executive Officer

Date: 12/20/2017

Date: 12/20/2017

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**AMENDMENT #3 TO AMENDED AND RESTATED PATENT LICENSE AGREEMENT**

This Amendment #3 (“**Amendment**”) to the ARPLA (as defined below) is made and entered into as of the date of last signature below (“**Amendment Effective Date**”) by and between **Aeglea BioTherapeutics Inc.**, a Delaware corporation, with its principal place of business at 901 S. MoPac Expressway, Barton Oaks Plaza One, Suite 250, Austin, Texas 78746 (“**Licensee**”) and the **University of Texas at Austin**, on behalf of the Board of Regents of the University of Texas System, an agency of the State of Texas, having its principal place of business at 2935 W. Braker Lane, Suite 1.9A (R3500), Austin, Texas 78759 (“**Licensor**”), each a “**Party**” and collectively, “**Parties**”.

**Background**

A. Licensor and Licensee entered into an Amended and Restated Patent License Agreement (UTA No. PM1401501) effective as of January 31st, 2017, as amended by Amendment #1 (UTA No. PA1401502) effective as of August 10, 2017 and Amendment #2 (UTA No. PA1401503) effective as of December 20, 2017 (collectively, the “**ARPLA**”).

B. Licensor and Licensee wish to amend the ARPLA as set forth below in order to update the list of Patent Rights and reference an additional sponsored research agreement between the Parties;

NOW, THEREFORE, in consideration of the mutual covenants and promises herein contained, the Parties hereby agree as follows:

1. **Intent.** Except as expressly provided in this Amendment, the ARPLA will remain unchanged and in full force and effect in accordance with its original terms. Capitalized terms used herein without definition shall have meanings given to them in the ARPLA.
2. **Section 1, Patent Rights Table.** In Section 1 of the ARPLA, the Patent Rights table shall be deleted in its entirety and replaced with the following:

<b>Patent Rights</b>				
<b>App. No./ Date of Filing</b>	<b>Title</b>	<b>Inventor(s)</b>	<b>Jointly Owned? (Y/N; if Y, with whom?)</b>	<b>Prosecution Counsel</b>
US 61/871,727 filed 8/29/2013	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
US 61/948,106 filed 3/05/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC

US 14/472,779 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
South Korea 10-2016-7008299 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
PCT/US2014/053374 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
JP 2016-537886 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Israel 244263 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Europe 14839001.6 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
China 201480054224.9 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Canada 2,922,557 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
Australia 2014312168 filed 8/29/2014	Engineered Primate Cystine/Cysteine Degrading Enzymes as Antineogenic Agents (6337 GEO)	George Georgiou Everett M. Stone	No	Parker Highlander PLLC
US 61/871,768 filed 8/29/2013	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
US 14/472,750 Issued as 9,481,877 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC

US 15/297,102 Issued as 9,624,484 filed 10/18/2016	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
US 15/451,349 filed 3/06/2017	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
South Korea 10- 2016-7007045 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
PCT/US2014/053359 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
JP 2016-537882 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Israel 244261 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Europe 14841106.9 filed 8/29/2014  Issued as 3039139 on 10/10/2018	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
China 201480050681.0 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
Canada 2,922,550 filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC

Australia 2014312159  filed 8/29/2014	Engineered Primate L-Methionase for Therapeutic Purposes (6314 GEO)	George Georgiou Everett M. Stone Wei-Cheng Lu	No	Parker Highlander PLLC
US Provisional 62/505,527  filed 5/12/2017	Engineered Primate Cystine/Cysteine Degrading Enzymes For Therapeutic Uses (6848 GEO)	George Georgiou Everett M. Stone Shira Cramer	No	Parker Highlander PLLC
US 15/977,246  Filed 5/11/2018	Engineered Primate Cystine/Cysteine Degrading Enzymes For Therapeutic Uses (6848 GEO)	George Georgiou Everett M. Stone Shira Cramer	No	Parker Highlander PLLC
PCT application PCT/US2018/032286  Filed 5/11/2018	Engineered Primate Cystine/Cysteine Degrading Enzymes For Therapeutic Uses (6848 GEO)	George Georgiou Everett M. Stone Shira Cramer	No	Parker Highlander PLLC
US Provisional 62/359,018  filed 7/06/2016	Human-Enzyme Mediated, Depletion of Cystine for Treating Patients with Cystinuria (6961 STO)	Everett M. Stone	No	Parker Highlander PLLC
US 15/643,436  filed 7/06/2017	Human-Enzyme Mediated, Depletion of Cystine for Treating Patients with Cystinuria (6961 STO)	Everett M. Stone	No	Parker Highlander PLLC
PCT application PCT/US2017/040897  filed 7/06/2017	Human-Enzyme Mediated, Depletion of Cystine for Treating Patients with Cystinuria (6961 STO)	Everett M. Stone	No	Parker Highlander PLLC
US Provisional 62/505,493  filed 5/12/2017	Human-Enzyme Mediated, Depletion of Homocysteine for Treating Patients with Homocysteinemia/Homocystinuria (7078 STO)	Everett M. Stone George Georgiou	No	Parker Highlander PLLC
PCT application PCT/US2018/032246  filed 5/11/2018	Human-Enzyme Mediated Depletion Of Homocysteine For Treating Patients With Hyperhomocysteinemia And Homocystinuria (7078 STO)	Everett M. Stone George Georgiou Wei-Cheng Lu	No	Parker Highlander PLLC
US 15/977,299  filed 5/11/2018	Human-Enzyme Mediated Depletion Of Homocysteine For Treating Patients With Hyperhomocysteinemia And Homocystinuria (7078 STO)	Everett M. Stone George Georgiou Wei-Cheng Lu	No	Parker Highlander PLLC

US Provisional 62/751,197  filed 10/26/2018	ENGINEERED PRIMATE CYSTINE/CYSTEINE DEGRADING ENZYMES FOR THERAPEUTIC USES (7387 STO)	Everett M. Stone Wei-Cheng Lu Christos Karamitros	No	Parker Highlander PLLC
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3. **Section 20.3.** Section 20.3 of the ARPLA shall be deleted in its entirety and replaced by the following:

20.3 If the Parties mutually determine that the rights granted by this Patent License Agreement are essential to the Licensee's use of any University Invention arising under Sponsored Research Agreement UTA13-001113 or Sponsored Research Agreement UTA18-001200, then such University Invention shall be included in this Patent License Agreement, upon Licensee's payment to Licensor of a fee of \$10,000.

[SIGNATURE PAGE TO FOLLOW]

IN WITNESS THEREOF, Licensor and Licensee have entered into this Amendment effective as of the Amendment Effective Date.

THE UNIVERSITY OF TEXAS AT AUSTIN ON BEHALF OF THE  
BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM

AEGLEA BIOTHERAPEUTICS, INC

By: /s/ Les Nichols  
Les Nichols  
Interim Director  
Office of Technology Commercialization

By: /s/ Anthony Quinn  
Anthony Quinn, Ph.D.  
CEO

Date: 11/27/2018

Date: 12/6/18

Licensee: Aeglea BioTherapeutics, Inc.  
The University of Texas at Austin  
US 4915892v.1

8  
CONFIDENTIAL

Exclusive PLA  
Agreement No. PM1401501

[\*] Certain confidential information contained in this document, marked by brackets, has been omitted and filed separately with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934, as amended.

**DATED**

**November 7, 2018**

**(1) FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LIMITED**

**(2) FUJIFILM DIOSYNTH BIOTECHNOLOGIES TEXAS, LLC**

**(3) FUJIFILM DIOSYNTH BIOTECHNOLOGIES U.S.A., INC**

**AND**

**(4) AEGLEA BIOTHERAPEUTICS, INC.**

**MASTER SERVICES AGREEMENT**

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**FUJIFILM**

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**THIS AGREEMENT** is made on the date set out above.

**BETWEEN**

- (1) **FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LIMITED** incorporated and registered in England and Wales with company number 05803359 whose registered office is at Belasis Avenue, Billingham, TS23 1LH, England ("**FDBK**");
- (2) **FUJIFILM DIOSYNTH BIOTECHNOLOGIES TEXAS, LLC** incorporated and registered in Texas whose principal place of business is at 100 Discovery Drive, Suite 200 College Station, Texas 77845 United States of America ("**FDBT**");
- (3) **FUJIFILM DIOSYNTH BIOTECHNOLOGIES U.S.A., INC** incorporated and registered in Delaware whose principal place of business is at 101 J Morris Commons Lane, Morrisville, North Carolina 27560, United States of America ("**FDBU**"); and
- (4) **AEGLEA BIOTHERAPEUTICS, INC.** incorporated and registered in Delaware whose principal place of business is at 901 S. Mopac Expressway, Barton Oaks Plaza One, Suite 250, Austin, TX 78746 (the "**Customer**").

**BACKGROUND**

- (A) Fujifilm (as defined below) is a biopharmaceutical contract development and manufacturing organization. The Customer wishes to appoint Fujifilm to carry out development and manufacturing services in relation to certain of the Customer's products.
- (B) Fujifilm and the Customer have agreed to work together on the terms and conditions contained in this Agreement.

**AGREED TERMS**

**1. DEFINITIONS AND INTERPRETATION**

1.1 In this Agreement the following words have the following meanings unless inconsistent with the context:

- "Affiliate"** in respect of any party, any company from time to time directly or indirectly Controlling, Controlled by or under common Control with that party;
- "Ancillary Services"** has the meaning given to it in Schedule 1 (Charges);
- "Applicable Laws"** applicable law, rules, regulations and binding guidance which applies in the jurisdiction in which the Program being performed;

<b>“Background IP”</b>	<p>all Intellectual Property Rights controlled, owned or jointly owned by any party (or a third party on its behalf prior to the Effective Date or developed independently from the Program. Fujifilm’s proprietary manufacturing expression or purification technologies, including:</p> <p>(a)an expression system within the scope of international patent application PCT/GB2007/00035 (the “pAVEway™ Expression System”);</p> <p>(b)expression technology within the scope of international patent application PCT/GB2014/00016 (the “Apollo™ Expression Technology”); and</p> <p>(c)Fujifilm’s proprietary alcohol oxidase yeast <i>Pichia pastoris</i> expression system (the “Yeast Expression System”),</p> <p>(collectively, “<b>Fujifilm Expression Technology</b>”) is Fujifilm’s Background IP;</p>
<b>“Batch”</b>	<p>a quantity of Product that is produced from a run of the Process;</p>
<b>“Batch Cancellation Fee”</b>	<p>the Batch Cancellation Fee described in Schedule 1;</p>
<b>“Business Day”</b>	<p>(a)in relation to notices given under this Agreement rather than a specific Scope of Work a day other than a Saturday, Sunday or public holiday in England or the US; and</p> <p>(b)in relation to notices given under a specific Scope of Work a day other than a Saturday, Sunday or public holiday in England if FDBK is a contracting party or the US if FDBT or FDBU is a contracting party;</p>
<b>“cGMP”</b>	<p>Current Good Manufacturing Practice as defined in (i) the Federal Register volume 66 No 186 and those sections applicable within the FDA Regulations 21 CFR Part 210, 211, 600, 601 and 610 and (ii) the rule governing medicinal products in the European Union. Volume 4 – Guidelines for good manufacturing practice for medicinal products for human and veterinary use, as applicable to the Program and ICHQ7;</p>
<b>“cGMP Batch”</b>	<p>a Batch identified in a Scope of Work which is intended to be manufactured during a Manufacturing Stage and subject to Disposition in each case in accordance with cGMP;</p>
<b>“Change”</b>	<p>has the meaning given to it in clause 13;</p>
<b>“Charges”</b>	<p>has the meaning set out in clause 8.2;</p>
<b>“Commercially Reasonable Efforts”</b>	<p>with respect to the activities pursuant to a Program, the reasonable efforts and resources used by a reputable biopharmaceutical contract manufacturing organization for drug substances of similar nature, complexity and developmental stage in the same or similar circumstances;</p>

**“Confidential Information”** the fact and terms of this Agreement and any Scope of Work, and all information (in whatever form in respect of the business of each of the parties and each of its Affiliates including any idea; technologies; business methods; finance; prices, business, financial, marketing or development plans; products or services, know-how or other matters connected with products or service manufactured and/or marketed; customer lists or details; computer systems and software; which in each case) provided or obtained

by one party to or for the other; notwithstanding anything to the contrary herein;

(a) Results, information regarding Materials, and Customer’s business, scientific, research, and development plans; and

(b) for the purposes of Clause 12, Customer Foreground IP;

shall be deemed solely Customer’s Confidential Information, and with respect to which, Customer shall be the Disclosing Party and Fujifilm the Receiving Party;

**“Conforming Batch”** a cGMP Batch which has been produced in accordance with cGMP and which meets the Product Specification;

**“Consumable”** a consumable item used or intended for use in a Program, including PEG, reagents (including analytical reagents), raw materials, packaging components, chromatography resins, filters, filtration membranes, media buffer bags, re-fold bags, tubing, hoses, disposable analytical test kits, in-process measurement probe columns (including analytical columns) and disposable containers;

**“Control”** (a) any power (whether directly or indirectly and whether by the ownership of share capital, the possession of voting power, contract or otherwise) to appoint and/or remove all or such of the members of the board or other governing body of a body corporate as are able to cast the majority of the votes capable of being cast by members of that board or body on all, or substantially all, matters, or otherwise to control or have the power to control the policies and affairs of that body corporate; or

(b) the holding and/or possession of the beneficial interest in and/or the ability to exercise the voting rights applicable to shares or other securities in any person (whether directly or indirectly) which confer aggregate on the holders thereto 50% or more of the total voting rights exercisable at general meetings of that body corporate on all, or substantially all, matters,

and **“Controlled”** and **“Controlling”** shall be construed accordingly;

**“Customer Foreground IP”** all Foreground IP other than Fujifilm Foreground IP;

**“Delay”** has the meaning given to it in clause 14.1.1;

**“Demonstration Batch”** a Batch which is manufactured in a noncGMP R&D facility for demonstration purposes and which is not intended for human use;

**“Deviation”** a cGMP deviation as detailed in the Quality Agreement;

**“Disposition”** the Stage during which (i) the Product is tested for compliance versus the Product Specification; (ii) a production instruction and analytical records relating to cGMP manufacture of each cGMP Batch prepared by Fujifilm are reviewed; and (iii) a Fujifilm recommendation for Product release or reject is made; in each case as applicable;

<b>“Drug Product”</b>	the final dosage form of product which contains Product in association with other active or inactive ingredient
<b>“Effective Date”</b>	the date of last signature by all parties to this Agreement;
<b>“Engineering Batch”</b>	a Batch that is manufactured in a cGMP Facility at scale using the Process including draft batch records but which is not intended for human use;
<b>“Facility”</b>	any of Fujifilm's manufacturing facilities in which a Program will be performed;
<b>“Force Majeure Event”</b>	any event or circumstances outside the reasonable control of a party affecting its ability to perform any of its obligations under this Agreement including act of God, fire, flood, severe weather, epidemic or pandemic, war, revolution, acts of terrorism, riot or civil commotion, acts of government, trade embargo, labor dispute (excluding labor disputes involving the party in question), interruption of utility service, restraints or delay affecting shipping or carriers, inability or delay in obtaining supplies of adequate or suitable material, breakdown or failure in equipment or machinery, cyber-attack, currency restrictions, and illness affecting a material number of the Program team, but shall not include the failure of Drug Product in clinical trials or failure of Drug Product to gain regulatory approval;
<b>“Foreground IP”</b>	all Intellectual Property Rights that arise or are obtained or developed by or on behalf of any party in the course of the performance of a Program;
<b>“Fujifilm”</b>	FDBK, FDBT and/or FDBU as the context requires in accordance with clause 1.3;
<b>“Fujifilm Foreground IP”</b>	all Foreground IP that (i) can be generally applied to the production of biologics other than the Product, and (ii) are not specific to or do not require the use of any of Customer's Confidential Information;
<b>“Fujifilm Services”</b>	the research and development services to be provided by Fujifilm for the Customer during a Program as the same are described in the relevant Scope of Work excluding the Ancillary Services;
<b>“Indemnify”</b>	on demand to indemnify and keep indemnified, and hold harmless, the party to be indemnified on an after the fact basis;
<b>“Intellectual Property Right”</b>	any current and future intellectual property rights and interests including patents, utility models, design rights, design rights, copyright (including rights in software), decryption rights, database rights, trade marks, rights pursuant to passing off, service marks, business and trade names, domain names, know-how, results, data, databases, formulations, compounds, rights in biological or chemical materials, rights under data exclusivity laws, rights under unfair competition laws, topography rights, inventions, rights in confidential information (including technical and commercial trade secrets); supplementary protection certificates and image rights, and rights of a similar or corresponding character in any part of the world, in each case whether registered or not and including any application for registration and renewals or extensions of such rights in any country in the world and whether subsisting now or in the future;

<b>“Latent Defect”</b>	a defect in a Batch that Sponsor can demonstrate was present at the time of Disposition but was discovered after Disposition (but within the time frame set forth in <u>Section 6</u> ) that renders the Batch as Non-Conforming Batch. Inherent stability or instability of a Product shall never give rise to a Latent Defect. Furthermore defects caused by Customer’s handling, transportation or storage of the Product shall never give rise to Latent Defect.
<b>“Liabilities”</b>	any (i) liabilities whether in contract, tort (including negligence) or otherwise; (ii) losses, costs (including internal costs/overheads), damages, fines or expenses, including reasonable legal fees; and (iii) claim demand, proceeding, action or cause of action; in each case howsoever arising. <b>“Liability”</b> shall be construed accordingly;
<b>“Manufacturing Stage”</b>	a Stage of a Program during which production, testing and Disposition (if applicable) of Engineering Batches and cGMP Batches are intended to take place, including pre and post manufacturing activities; Facility change over, setup, and cleaning before, between and after Batch manufacturing;
<b>“Modifications”</b>	a modification to a Facility; or equipment (including Process specific qualification and installation of existing equipment), required in order to perform a Process and detailed in the applicable Scope of Work;
<b>“Non-Conforming Batch”</b>	a cGMP Batch which has not been produced in accordance with cGMP and/or does not meet the Product Specification;
<b>“Non-Manufacturing Stage”</b>	a Stage of a Program, which is not a Manufacturing Stage, during which the non-manufacturing activities described in the relevant SoW are undertaken including the production and testing of Demonstration Batches
<b>“Process”</b>	a particular process used, or to be used, for manufacture of a Product;
<b>“Process-Specific Consumable”</b>	a Consumable which is required to operate the Process and which is specific to the Process or a Consumable which is required in such large volumes as would not be possible for Fujifilm to consume during other manufactures and/or within the shelf life of such Consumable;
<b>“Process-Specific Equipment”</b>	an item of equipment which is required by Fujifilm to operate the Process and which is specific to the Process in addition to that equipment which Fujifilm uses in its Facilities as at the SoW Effective Date (which existing equipment is not already dedicated to other customer(s) of Fujifilm);
<b>“Product”</b>	the particular product or substance (compound or molecule) created during and as a result of performing the Process. The name of relevant Product is identified in the applicable Scope of Work;
<b>“Product Specification”</b>	the Product specification which is documented in a QA Document;
<b>“Program”</b>	a program of work as set out in the applicable Scope of Work (or more than one Scope of Work, as the case may be) to be carried out by Fujifilm in accordance with the terms of this Agreement;
<b>“Program Cancellation Fee”</b>	the Program Cancellation Fee described in Schedule 1;
<b>“Program Manager”</b>	the Program manager appointed by each of Fujifilm and the Customer under the applicable SoW;

<b>“Program Plan”</b>	the Program plan controlled by Fujifilm’s Program Manager and communicated to the Customer from time to time;
<b>“Quality Agreement”</b>	the document agreed by the parties which sets out the mutually agreed quality standards applicable for an cGMP or pre-cGMP activity under the Program;
<b>“QA Documents”</b>	the Quality Agreement and the documents produced and approved in accordance with the Quality Agreement
<b>“Results”</b>	all data and tangible property obtained or generated by Fujifilm in the course of providing the Programs ( arising out of the use of Customer’s Confidential Information);
<b>“Regulatory Authority”</b>	the U.S. Food and Drug Administration, the European Medicines Agency, the Medicines & Healthcare products Regulatory Agency, and any successor to any such entities;
<b>“Scope of Work” or “SoW”</b>	the document setting out the detail of the work to be undertaken by Fujifilm for the Customer;
<b>“SoW Effective Date”</b>	for each Scope of Work, the date that the Scope of Work is fully signed by all relevant parties;
<b>“Special Waste”</b>	waste or effluent which requires special handling including waste or effluent which is required to be collected in a special container (for example by tanker) for external disposal or which requires incineration;
<b>“Stage”</b>	a stage of the Program as described in the SoW;
<b>“Subcontracted Work”</b>	work subcontracted by Fujifilm under clause 20.3 but excluding any work subcontracted between FDBK, FDB and/or FDBU;
<b>“Target Specifications”</b>	With respect to a Demonstration Batch or Engineering Batch, the Product Specifications for safety with regard to bioburden and endotoxin and identity of the Product as mutually agreed by the parties and set forth in the batch records.
<b>“Tax”</b>	value added tax, sales tax or any other similar type of turnover tax; and

**“Unforeseen Technical Factor”**

either (i) a change to Applicable Laws which comes into effect after the applicable SoW Effective Date or (ii) an event or circumstance (not caused by a breach by Fujifilm of clause 4.1) which:

(a) adversely affects the development of the Process; or

(b) adversely affects, or is likely to adversely affect, production of Product by the Process when conducted in accordance with Fujifilm’s standard operating procedures or methods, and within the declared constraints of the Facility; or

(c) is likely to have an adverse effect on any customer Product Licence (being the licence authorising marketing of a medicinal product granted by a Regulatory Authority (also known as a “Marketing Authorisation” in Europe)) or Manufacturing Licence (being the licence to manufacture biotechnology-derived drug substances issued to Fujifilm by the applicable Regulatory

Authority) as a result of the Product being introduced into the Facility,

which in each case was not known by Fujifilm and could not reasonably have been known by Fujifilm as at the applicable SoW Effective Date.

1.2 In this Agreement (except where the context otherwise requires) any words following the terms “including”, “include”, “for example” or any similar expression are by way of illustration and emphasis only and shall not limit the generality or extent of any other words or expressions.

1.3 Each Scope of Work will be entered into by FBDK, FBBDT or FDBU or a combination of FBDK, FBBDT and/or FDBU and, subject to clause 18.3, each reference to Fujifilm or a “party” in this Agreement shall apply only to such of FBDK, FBBDT and/or FDBU as is carrying out the Program under the relevant Scope of Work. Whichever of FBDK, FBBDT and/or FDBU has entered into the Scope of Work in respect of that Program shall be fully and solely responsible for the obligations and liabilities of that party under the Scope of Work.

1.4 Insofar as this Agreement obliges any party to this Agreement to negotiate, take action or to do something, that party shall conduct such negotiations, take such action or do such thing in good faith and, in the case of Fujifilm, using Commercially Reasonable Efforts to achieve the result contemplated in this Agreement. There shall be a general obligation on the parties to act in good faith in relation to the matters contemplated in this Agreement.

1.5 In the case of conflict or ambiguity between terms of the main body of this Agreement, any Schedule to this Agreement or any other terms in any Scope of Work, the order of priority shall be as follows: (i) the main body of the Agreement; (ii) the Schedules to the Agreement; and (iii) the main body of the Scope of Work unless a Scope of Work specifically varies a provision of the Agreement or a Schedule to the Agreement by reference to the provision it is amending in which case the Scope of Work shall take precedence in that instance.

1.6 In the case of conflict or ambiguity between the terms of this Agreement or any specific Scope of Work and the terms of the QA Documents, the terms of the QA Documents shall prevail solely in relation to cGMP quality matters subject to clause 9.9.

1.7 Where a defined term is used in clause 9 (Liability) it shall retain its meaning even when the entire word that is a defined term is in capitals.

**2. APPOINTMENT OF FUJIFILM**

2.1 This Agreement establishes the general terms and conditions applicable to Fujifilm’s performance of each Program for the Customer and is structured so that a separate, numbered, Scope of Work (or in some cases multiple Scope of Works) shall be entered into by the parties for the provision of each Program.

2.2 The provisions of this Agreement shall apply to each Scope of Work and no Scope of Work shall be effective or binding on any party until it has been signed by an authorized representative of each contracting party.

2.3 Nothing in this Agreement or any Scope of Work shall oblige any party to enter into any Scope of Work and each Scope of Work constitutes a separate contract.

**3. TERM**

3.1 This Agreement shall come into force on the Effective Date and shall continue until terminated by a party in accordance with the terms of this Agreement.

3.2 A party may terminate this Agreement upon giving 6 (six) months’ written notice to the others, provided that there are no uncompleted Programs existing at the date such notice is given.

- 3.3 Each Scope of Work will take effect from the SoW Effective Date and shall continue until the earlier of:
  - 3.3.1 the date specified in the Scope of Work, or if no such date is specified, the date the Program, or part of the Program referred to in the Scope of Work is completed; or
  - 3.3.2 termination of this Agreement or the relevant Scope of Work in accordance with the terms of this Agreement.

**4. PERFORMANCE OF PROGRAMS**

- 4.1 Fujifilm shall carry out each Program:
  - 4.1.1 in accordance with the terms of this Agreement and any Scope of Work;
  - 4.1.2 in accordance with all Applicable Laws;
  - 4.1.3 in accordance with the Quality Agreement and cGMP (in both cases when applicable);
  - 4.1.4 in compliance with the Process when a Process has been mutually agreed by the parties;
  - 4.1.5 in a professional and workmanlike manner, in accordance with industry standards; and
  - 4.1.6 using Commercially Reasonable Efforts.
- 4.2 The parties agree that it shall not be considered a breach of this Agreement by Fujifilm if an objective of a Program is not achieved provided that Fujifilm has complied with its obligations set out in clause 4.1. Notwithstanding any contrary provisions in this Agreement, the parties acknowledge and agree that the services to be performed during the Programs are by their nature developmental and Fujifilm cannot (and consequently does not) guarantee to the Customer the achievement of a successful outcome for a Program, production of Conforming Batches or production of a specified volume of Product.
- 4.3 Upon request by the Customer, the parties agree to negotiate in good faith a commercial supply agreement with each other for the Product.
- 4.4 Each Scope of Work contains key assumptions on which Fujifilm's ability to perform the Program depends. If the key assumptions set out in the Scope of Work prove to be incorrect or actual circumstances differ from the key assumptions (including if such key assumptions cannot be met at such time as Fujifilm reasonably requires to enable it to perform its obligations) then the parties shall negotiate in good faith and agree a reasonable Change to account for the change in key assumptions. If the parties are unable to agree such Change and the dispute resolution process set out in clause 16 has been unsuccessfully exhausted Fujifilm may terminate the relevant SoW(s) and such termination shall be deemed to be for the Customer's convenience and clause 14.3 shall apply.
- 4.5 The Customer shall:
  - 4.5.1 meet all its obligations and responsibilities under this Agreement, any Scopes of Work and the Quality Agreement;
  - 4.5.2 comply with Applicable Laws; and

4.5.3 promptly provide all reasonable assistance, information, and advice and do all acts which Fujifilm may reasonably request to enable Fujifilm to comply with its obligations and responsibilities under this Agreement, any Scope of Work and the Quality Agreement.

4.6 Representations and Warranties:

4.6.1 Each party represents and warrants to the other party that:

(a) neither it nor any of its employees, or any agents are currently excluded, debarred, or otherwise made ineligible to participate in any federal health care program defined in 42 U.S.C. § 1320a-7b(f) (the "Federal Healthcare Programs"), any other government procurement or non-procurement program, or is subject to any penalty or exclusion imposed by the Food and Drug Administration. Fujifilm further represents and warrants that to its knowledge none of its subcontractors (including their employees) are currently excluded, debarred, or otherwise made ineligible to participate in any Federal Healthcare Programs, any other government procurement or non-procurement program, or is subject to any penalty or exclusion imposed by the Food and Drug Administration. Each party further represents and warrants to the other party that, to its knowledge, neither it nor any of its employees, or any agents or subcontractors (including their employees) (i) has been convicted of a criminal offense related to the provision of health care items or services but has not yet been excluded, debarred, or otherwise declared to be either ineligible to participate in the Federal Healthcare Programs or subject to any penalty or exclusion imposed by the Food and Drug Administration, or (ii) has been notified by a government agency of an investigation or other formal proceeding that may result in any criminal, civil, or administrative penalty involving the Federal Healthcare Programs or any exclusion or penalty imposed by the Food and Drug Administration. The parties further agree that this obligation shall continue throughout the term of this Agreement, that an affected party shall notify the other party immediately of any change in these representations and warranties of which it becomes aware and the other party shall have the immediate right to terminate this Agreement upon receipt of any such notice of change; and

(b) it has all requisite corporate power and authority to enter into and perform all of its obligations under this Agreement. The execution and delivery of this Agreement and the consummation of the transactions contemplated hereby have been duly and validly authorized by all necessary corporate action in respect thereof on the part of such party. Neither the execution and delivery of this Agreement nor the performance of the transactions contemplated hereby, nor compliance by Fujifilm with the provisions hereof, shall conflict with any obligations or agreements of such party to any person, contractual or otherwise

4.6.2 Customer represents and warrants to Fujifilm that it has legal title and/or a valid license to the cell line, raw material, expression systems, process patents and the Product necessary to conduct the Program and that to Customer's knowledge, Fujifilm's performance of the Program will not infringe any Intellectual Property Rights or other rights of third parties.

4.6.3 Fujifilm represents and warrants to the Customer that:

(a) All Product shall be manufactured in the Facility, unless mutually agreed otherwise;

(b) unless delivery of a Non-Conforming Batch is requested by Customer, Fujifilm shall not deliver a Non-Conforming Batch to Customer;

(c) Fujifilm has, and will remain in material compliance with, all permits, licenses and other authorizations (the "Permits") which are required under Applicable Laws for the manufacture, testing, storage, and/or handling of Product;

(d) to Fujifilm's knowledge, Fujifilm's use of Fujifilm's Background IP in the manufacture of Product in the performance of this Agreement will not infringe any Intellectual Property Rights or other rights of third parties; and

(e) upon payment pursuant to clause 8, title to all Product provided to the Customer hereunder shall pass to Customer as provided herein, free and clear of any security interest, lien, or other encumbrance.

5. **QUALITY AND REGULATORY MATTERS**

5.1 Quality Agreement

5.1.1 As soon as reasonably practicable following the Effective Date the parties shall execute the Quality Agreement (unless the Quality Agreement has already been executed prior to the Effective Date).

5.1.2 The Customer acknowledges that Fujifilm shall not commence any cGMP or pre-cGMP activity until the Quality Agreement is executed by both parties.

5.2 Regulatory Assistance

5.2.1 The Customer shall provide Fujifilm with a copy of the Customer's Chemistry, Manufacturing and Controls section of any submission to a Regulatory Authority supporting the Customer's regulatory filing activities for the applicable Drug Product or Process to the extent relating to or impacting Fujifilm ("**CMC Section**") for Fujifilm's review and comment before submission to such Regulatory Authority. Fujifilm shall provide any comments on the CMC Section to the Customer within such ten (10) day period, which the Customer shall consider in good faith before submission; if the Customer receives no such comments within such period, the CMC Section shall be deemed approved by Fujifilm.

5.2.2 During each Program the Customer may request assistance from Fujifilm in respect of the CMC Section, subject to payment by the Customer of a reasonable commercial rate for such assistance and Fujifilm's reasonable expenses. However, no advice or assistance given by Fujifilm shall be deemed to be or construed as a guarantee that a Drug Product will receive regulatory approval.

**\*Confidential Treatment Requested.**

Fujifilm shall use Commercially Reasonable Efforts to assist the Customer, which may be at Customer's cost, in connection with obtaining regulatory approvals in the United States and Europe with respect to the Product. Regulatory approvals in subsequent jurisdictions will be subject to a Change. Fujifilm will promptly [\*] provide one electronic (PDF) copy of any documents which may be reasonably required by the Customer in support of its regulatory filing activities. If the Customer requires copies of the laboratory notebooks, provision of these will be subject to discussion and agreement by the parties and agreement of an additional fee associated with copying.

5.2.4 The Customer shall have the right and responsibility for determining regulatory strategy, decisions and actions relating to each Program and any Product and/or Drug Product subject to clause 5.2.5 and provided that Fujifilm shall have the right and

responsibility for determining regulatory strategy, decisions and actions to the extent relating to:

- (a) the Facility (including in particular utilities and equipment);
- (b) Fujifilm's quality systems, policies and internal procedures;
- (c) any requirement imposed on Fujifilm by a Regulatory Authority; or
- (d) any other commitments made by Fujifilm prior to the relevant SoW Effective Date of the applicable Program,

(each a "**Fujifilm Regulatory Responsibility**").

5.2.5 The Customer acknowledges that Fujifilm Quality Assurance team reserves the right to Disposition Product to Customer in accordance with the Quality Agreement. Customer has the responsibility to determine whether to release cGMP Product for use in clinical trials.

5.2.6 The Customer shall not make any change to its regulatory filings, including its Investigational New Drug application, which may have a direct impact on any Fujifilm Regulatory Responsibility without prior written approval of Fujifilm, such approval not to be unreasonably withheld.

5.2.7 Fujifilm will allow representatives of any Regulatory Authority with jurisdiction over the manufacture, marketing, distribution and sale of the Product to tour and inspect the Facility, and will cooperate with such representatives in every reasonable manner.

## 6. **CONFORMING BATCHES, NON-CONFORMING BATCHES, DEMONSTRATION BATCHES AND ENGINEERING BATCHES**

6.1 Neither a Demonstration Batch nor an Engineering Batch can ever be a Non-Conforming Batch and the Customer shall pay for every Demonstration Batch and Engineering Batch completed [\*]. Product produced pursuant to a Demonstration Batch or an Engineering Batch is not suitable for human consumption or use or clinical trials.

6.2 Each cGMP Batch will be determined to be a Conforming Batch or a Non-Conforming Batch.

6.3 If during a Manufacturing Stage relating to a cGMP Batch Fujifilm discovers any significant Deviation it will be handled in accordance with the Quality Agreement. The Customer agrees that only Deviations, alone or in combination, which are determined or reasonably considered to affect Product quality will cause a cGMP Batch to be classified as a Non-Conforming Batch.

6.4 In respect of Conforming Batches, Fujifilm will complete Disposition, issue a certificate of analysis and a cGMP compliant statement, and provide additional documentation as agreed upon in the Quality Agreement. The provisions of clauses 6.5 to 6.7 shall apply to Non-Conforming Batches only.

### **\*Confidential Treatment Requested.**

If a Batch is a Non-Conforming Batch and the cause of that Batch being a Non-Conforming Batch is not a failure by Fujifilm to comply with clause 4.1, then the Customer shall pay the Charges relating to the Non-Conforming Batch in full and the relevant Manufacturing Stage, Disposition and all related and ancillary activities shall be deemed to have been completed under the Scope of Work. Further work in relation to the Non-Conforming Batch, such as analysis of the Batch, shall be promptly performed and reported. If requested by Customer, manufacture of a replacement cGMP Batch shall be carried out at a time and price to be agreed in writing by the parties in a Change.

6.6 Except as set forth in Section 6.6.3, if a Batch is a Non-Conforming Batch and the cause of the Batch being a Non-Conforming Batch is a failure by Fujifilm to comply with clause 4.1, then either:

6.6.1 if the Customer requests delivery of the Non-Conforming Batch, the parties shall agree in writing (in a Change) on fair consideration payable under the Scope of Work in respect of that Batch, and Fujifilm's obligation in relation to that Batch shall be deemed to be completed when such Change is signed and that Batch is delivered; or

if the Customer does not request delivery of the Non-Conforming Batch, at the Customer's option, Fujifilm shall use Commercially Reasonable Efforts to manufacture a replacement cGMP Batch ("**Replacement Batch**") as soon as is reasonably practicable at no additional cost to Customer (though Customer shall be obliged to pay for all Charges in respect of the original Non-Conforming Batch in accordance with the SoW), plus the Charges for the Ancillary Services provided in relation to the Replacement Batch[\*]

**\*Confidential Treatment Requested.**

6.6.3 In the event the first Batch of a Program is a cGMP Batch not preceded by an Engineering Batch, Fujifilm shall be responsible under this Section 6.6 for the first such cGMP Batch being a Non-Conforming Batch only if the non-conformance is caused by Fujifilm's gross negligence or willful misconduct.

6.7 In the event of a Latent Defect, Customer shall notify Fujifilm of such Latent Defect within the earlier of (a) [\*] after discovery of the Latent Defect and (b) [\*] after Disposition. If the cause of the Latent Defect is a failure by Fujifilm to comply with clause 4.1, Section 6.6 shall apply.

6.8 In case of any disagreement between the parties as to whether a cGMP Batch is a Non-Conforming Batch and the cause of a Non-Conforming Batch, the respective quality assurance representatives of the parties will attempt in good faith to resolve any such disagreement and the Customer and Fujifilm will follow their respective standard operating procedures to determine whether the Batch is a Non-Conforming Batch and if a Non-Conforming Batch, whether it was caused by Fujifilm's failure to follow Section 4.1. In the event such activities do not resolve the issue, the Parties shall follow the dispute resolution process set forth in the Quality Agreement.

6.9 If the Customer requires delivery of a Non-Conforming Batch it must make such request to Fujifilm in writing within [\*] of being informed that the Batch is a Non-Conforming Batch. Fujifilm agrees to deliver a Non-Conforming Batch to the Customer on the express condition that it (i) will not be used for human or clinical trials; (ii) will be labeled as "Not for Human Use"; and (iii) is subject to the Customer's indemnity given under clause 9.5.

**7. DELIVERY, TITLE AND RISK**

7.1 Delivery by Fujifilm to the Customer of any material in connection with the Program including any quantity of Product manufactured during the Program, any Process-Specific Equipment and/or Process-Specific Consumables and return of any samples, cell lines and other materials supplied by the Customer ("**Materials**") will be made Ex Works the Facility (Incoterms 2010) and clauses 7.2 to 7.5 shall apply to such Materials. Fujifilm shall package the relevant Material ready for shipment in accordance with the Customer's reasonable instructions. Except to the extent set forth in Section 3.4 of Schedule 1, Fujifilm shall use Materials only for the purpose of performing the Programs and shall not subject such Materials to any analysis or use inconsistent with the Programs. Except to the extent set forth in Section 3.4 of Schedule 1, in no event shall Fujifilm use Materials for its own benefit or in connection with the performance of services for third parties.

7.2 Delivery of Materials will be deemed to be completed at the time at which Fujifilm makes the Materials available for collection by the Customer (which is the point of delivery as set forth in Ex Works (Incoterms 2010)).

If the Customer fails to collect Materials that have been deemed to be delivered under clause 7.2, Fujifilm shall provide notice to Customer and if Customer does not arrange for collection within [\*] Fujifilm may, at its discretion, either arrange for delivery of the Materials to the Customer at the Customer's risk and expense or destroy those Materials.

**\*Confidential Treatment Requested.**

7.4 Risk in the Material shall pass to the Customer on the completion of actual delivery.

7.5 Title to the Product shall pass to the Customer on delivery.

7.6 Title to the Process-Specific Equipment and/or Process-Specific Consumables purchased by the Customer in accordance with Schedule 1 shall not pass to the Customer until Fujifilm has received payment in full (in cash or cleared funds) for such items in accordance with paragraph 3.1 of Schedule 1.

7.7 Delivery of any Materials which the Customer is required to supply to Fujifilm pursuant to the SoW shall be delivered to Fujifilm DDP, the Facility (Incoterms 2010). Title to Materials provided by Customer shall remain vested in Customer. Fujifilm shall at all times use reasonable efforts to keep such Materials secure and safe from loss or damage. Subject to the limitations of liability set forth below, Fujifilm shall be liable for loss or damage to such Materials resulting from its gross negligence or intentional misconduct. Customer grants Fujifilm the right to use such Materials solely to the extent required to perform the any Program.

**8. PRICE AND PAYMENT**

8.1 Under this Agreement, and the relevant Scope of Work, the Customer appoints Fujifilm to carry out services concerning the research and development, testing, manufacture and Disposition of the Product by Fujifilm under a Program. The Charges relate specifically to those services; and are not in consideration of the supply of any material (including Product) which Fujifilm may produce as a consequence of the performance of those services.

8.2 The Customer shall pay to Fujifilm for each Program:

8.2.1 the fees for the Fujifilm Services as set out in the relevant Scope of Work; and

8.2.2 the fees for Ancillary Services in accordance with Schedule 1,

together the "**Charges**".

8.3 Fujifilm may invoice the Customer for the Charges in respect of each Program in accordance with the terms set out in the Scope of Work and Schedule 1. Fujifilm shall also use Commercially Reasonable Efforts to invoice the Customer for all taxes due with respect to the Charges, provided that Fujifilm shall be responsible for all taxes relating to its revenue derived under this Agreement.

8.4 The Customer shall pay all invoiced, undisputed amounts within 30 (thirty) days of receipt of invoice, in full and in cleared funds in the currency specified in the SoW by electronic transfer to the financial institution specified in the relevant invoice.

8.5 The Charges are exclusive of any Tax which may apply and which shall be payable by the Customer to Fujifilm at the rate prescribed by law.

8.6 If there is a change in the rate of Tax payable or in the Tax treatment of some or all of the services provided by Fujifilm or the Product, a change of law or practice or interpretation of the existing legislation or revised determination by HMRC (Her Majesty's Revenue and Customs) or the IRS (Internal Revenue Service), or the supply of services by Fujifilm has been incorrectly regarded as Tax exempt, or if the courts rule Tax is chargeable, then the Customer agrees that Fujifilm shall be entitled, where Tax is imposed on a supply by Fujifilm under or in connection with this Agreement (including the retrospective application of Tax upon services which Fujifilm has already performed and which have previously been invoiced on a Tax exempt basis), to invoice the Customer (in a valid Tax invoice) for a sum equal to the amount of the Tax which

becomes due on that supply and any fees and/or interest which HMRC and/or the IRS levies on Fujifilm in relation to the outstanding sums and/or non-payment. The Customer shall pay those invoices in accordance with clause 8.4.

8.7 The Customer shall:

8.7.1 be responsible for the collection, remittance and payment of any or all taxes, charges, levies, assessments and other fees of any kind imposed by governmental or other authority in respect of the purchase, importation, exportation, sale or other distribution of any materials delivered to it by Fujifilm in connection with the Program; and

8.7.2 make all payments under this Agreement without withholding or deduction of, or in respect of, any tax unless required by law. If any such withholding or deduction is required, the Customer shall, when making the payment to which the withholding or deduction relates, pay to Fujifilm such additional amount as will ensure that Fujifilm receives the same total amount that it would have received if no such withholding or deduction had been required.

8.8 Without prejudice to any other right or remedy that it may have, if the Customer fails to pay any invoiced, undisputed amounts to Fujifilm on the due date for payment:

the Customer shall pay interest on the overdue amount at the rate of [\*] per month. Such interest shall be payable in respect of the period from the due date until actual payment of the overdue amount (whether before or after judgment) in accordance with clause 8.4; and

**\*Confidential Treatment Requested.**

8.8.2 (except where the Customer has complied with its obligations in clause 8.9 below) Fujifilm may notify the Customer that if it does not pay Fujifilm will suspend work on the Program in respect of which payment is overdue, and if payment is not made within [\*] of such notice, Fujifilm may suspend such work until payment has been made in full.

8.9 If the Customer disputes the payment of any Charges or a part of them, the Customer shall:

8.9.1 notify Fujifilm of the disputed amount within [\*] of its receipt of the invoice in which such disputed amount is included giving reasonable details of the dispute; and

8.9.2 pay the amount of Charges not in dispute in accordance with clause 8.4,

and the dispute shall be dealt with under the dispute resolution process set out in clause 16.

8.10 If the Customer fails to pay any invoiced amount which is not the subject of a bona fide dispute under clause 8.9 when the same is due in accordance with clause 8.4 then Fujifilm may elect, at its discretion and [\*], to treat such non-payment as a material breach of either the relevant SoWs under clause 14.5.1 or a material breach of this Agreement under clause 14.2.1.

8.11 A party shall not be entitled to withhold, set off or reduce payment of any amounts payable under this Agreement by any amounts which it claims are owed to it by another party under this Agreement or any other agreement.

**9. LIABILITY**

9.1 The parties agree that:

9.1.1 the potential extent of Liability arising from the Programs and the Product are each better known to the Customer than to Fujifilm;

9.1.2 the potential extent of such Liability is disproportionate to the amounts which Fujifilm can reasonably charge for its performance of the Programs;

9.1.3 the Customer is better able to, and should, insure against any Liabilities the Customer might suffer,

and that consequently Fujifilm should restrict its Liability as set out in this clause 9 and the Customer should Indemnify Fujifilm in accordance with clauses 9.3, 9.4, 9.5.3, and 9.6.3 and the parties agree that clause 9.2 does not limit or exclude the Customer's Liability to Fujifilm under those indemnities.

9.2 SAVE THAT NOTHING IN THIS AGREEMENT LIMITS OR EXCLUDES THE LIABILITY OF ANY PARTY TO THE OTHER FOR ANY LIABILITY THAT IS NOT PERMITTED TO BE LIMITED OR EXCLUDED BY LAW:

9.2.1 EXCEPT WITH REGARD TO BREACHES OF CLAUSES 10 OR 12, IN NO EVENT SHALL A PARTY BE LIABLE TO ANY OTHER PARTY FOR ANY SPECIAL, INDIRECT, INCIDENTAL, PUNITIVE OR CONSEQUENTIAL DAMAGES IN ANY WAY RELATED TO THIS AGREEMENT OR SUCH PARTY'S PERFORMANCE OF ITS OBLIGATIONS HEREUNDER.

[\*] FUJIFILM'S TOTAL LIABILITY, WHETHER OR NOT ARISING PURSUANT TO THE INDEMNITY, IN CONTRACT, TORT (INCLUDING NEGLIGENCE OR BREACH OF STATUTORY DUTY), MISREPRESENTATION, RESTITUTION OR OTHERWISE ARISING UNDER THIS AGREEMENT OR A SCOPE OF WORK OR IN CONNECTION WITH THE PERFORMANCE OR CONTEMPLATED PERFORMANCE OF THIS AGREEMENT OR A SCOPE OF WORK SHALL IN ALL CIRCUMSTANCES BE LIMITED AS FOLLOWS:

**\*Confidential Treatment Requested.**

(a) IN RESPECT OF ANY LIABILITY ARISING UNDER A SCOPE OF WORK, FUJIFILM'S LIABILITY TO CUSTOMER SHALL BE LIMITED [\*]; AND

(b) IN RESPECT OF ANY OTHER LIABILITY RELATING TO THIS AGREEMENT, FUJIFILM'S LIABILITY TO CUSTOMER SHALL BE LIMITED [\*].

9.2.3 [\*]

9.3 Liability for Product and Drug Product: the Customer shall Indemnify Fujifilm from and against all Liabilities directly related to any third party claim incurred by Fujifilm or its Affiliates arising out of or resulting from the use or resale of the Product or the Drug Product or any other deliverable arising out of the Program; provided, however, that the Customer shall have no obligation to Indemnify Fujifilm from such Liabilities to the extent they arose from the gross negligence or intentional misconduct of Fujifilm or Fujifilm's material breach of clause 4.6.3(b).

9.4 Liability for the Process: the Customer shall Indemnify Fujifilm from and against all Liabilities directly related to any third party claim incurred by Fujifilm or its Affiliates arising out of or resulting from the use or operation of the Process (or any part of the Process) except to the extent that Fujifilm is liable under clause 11.1; provided, however, that the Customer shall have no obligation to Indemnify Fujifilm from such Liabilities to the extent they arose from the gross negligence or intentional misconduct of Fujifilm.

9.5 Liability for Non-Conforming Batches:

9.5.1 THE PROVISIONS OF CLAUSE 6 SHALL APPLY TO NON-CONFORMING BATCHES AND FUJIFILM SHALL HAVE NO LIABILITY IN RESPECT OF NON-CONFORMING BATCHES EXCEPT TO COMPLY WITH CLAUSE 6.6.

9.5.2 FUJIFILM GIVES NO, AND DISCLAIMS ANY, WARRANTIES, UNDERTAKINGS OR SIMILAR TERMS WHATSOEVER (WHETHER AS TO COMPLIANCE WITH CGMP OR OTHERWISE) IN RESPECT OF NON-CONFORMING BATCHES OR THE USE BY THE CUSTOMER OF NON-CONFORMING BATCHES.

9.5.3 If the Non-Conforming Batch is delivered to the Customer pursuant to clause 6, the Customer shall fully Indemnify Fujifilm from and against all Liabilities directly related to any third party claim incurred by Fujifilm or its Affiliates arising out of or resulting from the use of that Non-Conforming Batch.

9.5.4 The Customer uses any material produced in a Non-Conforming Batch at its own risk and shall undertake such tests as are necessary in order to satisfy itself that such materials are fit for the purposes for which the Customer proposes to use such materials.

9.6 Liability for Demonstration and Engineering Batches

9.6.1 FUJIFILM GIVES NO, AND DISCLAIMS ANY, WARRANTIES, UNDERTAKINGS OR SIMILAR TERMS WHATSOEVER (WHETHER AS TO COMPLIANCE WITH CGMP OR OTHERWISE) IN RESPECT OF THE DEMONSTRATION BATCHES OR ENGINEERING BATCHES OR THE USE BY THE CUSTOMER OF AN ENGINEERING BATCH OR DEMONSTRATION BATCH.

9.6.2 FUJIFILM SHALL HAVE NO LIABILITY TO THE CUSTOMER IN CONNECTION WITH DEMONSTRATION BATCHES OR ENGINEERING BATCHES OR THE USE BY THE CUSTOMER OF THE DEMONSTRATION BATCHES OR ENGINEERING BATCHES.

9.6.3 The Customer shall fully Indemnify Fujifilm from and against all Liabilities directly related to any third party claim incurred by Fujifilm or its Affiliates arising out of or resulting from the use of the Demonstration Batches or Engineering Batches.

9.6.4 The Customer uses any material produced in a Demonstration Batch or Engineering Batch at its own risk and shall undertake such tests as are necessary in order to satisfy itself that such materials are fit for the purposes for which the Customer proposes to use such materials.

9.7 Fujifilm shall Indemnify the Customer from and against all Liabilities directly related to any third party claim incurred by the Customer or its Affiliates related to this Agreement to the extent they arose from the gross negligence or intentional misconduct of Fujifilm; provided, however, that Fujifilm shall have no obligation to Indemnify Customer from such Liabilities to the extent they arose from the gross negligence or intentional misconduct of Customer.

9.8 FUJIFILM GIVES NO, AND DISCLAIMS ANY, WARRANTIES, UNDERTAKINGS OR SIMILAR TERMS WHATSOEVER IN RESPECT OF ANY ADVICE OR ASSISTANCE GIVEN BY FUJIFILM IN CONNECTION WITH THE USE OF THE PRODUCT IN OR AS A DRUG PRODUCT (INCLUDING ADVICE OR ASSISTANCE RELATED TO ANY REGULATORY APPROVAL); AND FUJIFILM SHALL HAVE NO LIABILITY TO THE CUSTOMER IN CONNECTION WITH ANY SUCH ADVICE OR ASSISTANCE.

9.9 ALL WARRANTIES, CONDITIONS AND OTHER TERMS, EXPRESS (OTHER THAN THOSE SET OUT IN THIS AGREEMENT) OR IMPLIED, STATUTORY, CUSTOMARY OR OTHERWISE WHICH BUT FOR THIS CLAUSE 9 WOULD OR MIGHT SUBSIST IN FAVOR OF THE CUSTOMER, ARE (TO THE FULLEST EXTENT PERMITTED BY LAW) EXCLUDED FROM THIS AGREEMENT INCLUDING, IN PARTICULAR, ANY IMPLIED WARRANTIES RELATING TO MERCHANTABILITY, FITNESS FOR A PARTICULAR USE AND NON-INFRINGEMENT.

9.10 No claim for Liabilities incurred pursuant to the Quality Agreement may be made under the Quality Agreement by any party. Accordingly, performance of the Quality Agreement shall be deemed to be performance under the SoW to which the Quality Agreement relates and as such any breach of the Quality Agreement shall be deemed to be a breach of the relevant SoW and all Liabilities shall be construed and limited in accordance with this clause 9.

- 9.11 Each party agrees to take all reasonable steps to mitigate any Liabilities that it may seek to claim from the other under or in connection with this Agreement including pursuant to any Indemnity.
- 9.12 If a party is entitled to benefit from an Indemnity (the “**Indemnified Party**”) from another party (the “**Indemnifying Party**”) in accordance with this Agreement (an “**Indemnity Claim**”), the Indemnified Party shall promptly notify the Indemnifying Party in writing of the Indemnity Claim (providing all necessary details) and the Indemnifying Party shall at its own expense conduct all negotiations and any litigation arising in connection with the Indemnity Claim provided always that:
- 9.12.1 the Indemnified Party shall have the right to obtain separate legal counsel at its own expense if it so chooses;
  - 9.12.2 the Indemnifying Party shall consult the Indemnified Party on all substantive issues which arise during the conduct of such litigation and negotiations and shall consider the interests of the Indemnified Party in good faith;
  - 9.12.3 the Indemnifying Party shall not settle or compromise the Indemnity Claim without the Indemnified Party's prior written consent (not to be unreasonably withheld or delayed) and shall ensure that any settlement or compromise does not include a statement as to or an admission of fault, culpability or a failure to act by or on behalf of the Indemnified Party;
  - 9.12.4 the Indemnified Party shall not make any admissions or admit liability in relation to the Indemnity Claim or otherwise settle any Indemnity Claim without the written agreement of the Indemnifying Party; and
  - 9.12.5 the Indemnified Party shall fully cooperate and assist the Indemnifying Party, at the Indemnifying Party's cost and expense, in relation to the Indemnity Claim (without limiting the extent of the Indemnity).
- 9.13 Each party shall maintain in effect appropriate insurance for the term of the Agreement in amounts sufficient to meet its obligations under this Agreement. Each party shall notify the other parties in writing within thirty (30) days of any notice of cancellation or non-renewal of, or material change in, or claim against, its insurance coverage that could reasonably affect its obligations under this clause 9.13. Each party shall provide certificates of insurance to the other parties upon reasonable request. Each party's insurance coverage shall comply with Applicable Laws.
10. **INTELLECTUAL PROPERTY**
- 10.1 Subject to clause 10.2 no party shall acquire any right, title or interest in another party's Background IP.
- 10.2 The Customer grants to Fujifilm a royalty-free, worldwide license to use Customer's Background IP for the exclusive purpose of performance of the Program. Customer warrants that to its knowledge, the use by Fujifilm (or its Authorized Third Parties) of Customer's Background IP in accordance with this clause 10.2 shall not infringe any third party's Intellectual Property Rights.
- 10.3 Fujifilm shall not be obliged to deliver any materials (including any cell bank or cell paste) comprising Fujifilm Expression Technology unless and until a license is granted in writing on terms to be agreed under the relevant Background IP. Fujifilm shall be entitled to charge the Customer for storage of any such materials which would have been delivered under clause 7.2 if a license had been granted under this clause 10.3 until the time that such license is granted. Fujifilm has reviewed the manufacturing process for the Product and warrants that the Process and Product shall not comprise any Fujifilm Expression Technology unless specifically stated in the applicable SoW.

- 10.4 All title to and all rights and interest in any Customer Foreground IP and Results shall vest in Customer. Fujifilm hereby assigns to the Customer all title to and all rights and interest in any Customer Foreground IP and Results.
- 10.5 All title to and all rights and interest in any Fujifilm Foreground IP shall vest in Fujifilm. The Customer hereby assigns to Fujifilm all title to and all rights and interest in any Fujifilm Foreground IP.
- 10.6 If requested to do so by another party, each party shall at the expense of the requesting party execute all documents and do all such further acts as the requesting party may reasonably require to perfect the assignment and give testimony which may be necessary to apply for and obtain patent protection in any country under clause 10.4 or 10.5.
- 10.7 Fujifilm grants to Customer a royalty free, worldwide license to use the Fujifilm Foreground IP for the exclusive purpose of manufacturing the Product and performance of the Program.

11. **INTELLECTUAL PROPERTY INDEMNITY**

- 11.1 Fujifilm shall fully Indemnify the Customer from and against all Liabilities incurred by the Customer or its Affiliates arising out of any third party claim that Fujifilm's use of Fujifilm's Intellectual Property Rights in performing the Program infringes such third party's Intellectual Property Rights.
- 11.2 The Customer shall fully Indemnify Fujifilm from and against all Liabilities incurred by Fujifilm or its Affiliates arising out of any third party claim that:
  - 11.2.1 Fujifilm's use of (i) materials provided by the Customer to Fujifilm or (ii) Customer's Intellectual Property Rights, in accordance with this Agreement; or
  - 11.2.2 (excluding Liabilities in relation to which Fujifilm Indemnifies the Customer pursuant to clause 11.1) the development or manufacture of the Product and/or any other deliverables which are an output of the Program or the use of the Process in accordance with this Agreement,infringes such third party's Intellectual Property Rights.

- 11.3 If a third party claim is made in accordance with clause 11.1 or 11.2 then the Indemnified Party may require the Indemnifying Party to prove that it has reasonably adequate financial means to pay out under the indemnity provisions provided for in those clauses (for example by way of set aside capital or insurance). If the Indemnifying Party cannot so prove it has the reasonable financial standing to meet its obligations with respect to the Indemnities under the applicable clause then the Indemnified Party (a) may immediately suspend performance of all obligations (other than payment obligations) under this Agreement and SOW and (b) has the option to terminate this Agreement on thirty (30) days' prior written notice. If Fujifilm exercises its option to terminate under this clause 11.3 then (without prejudice to the survival of the relevant Indemnity obligations) such termination shall be treated as a termination under clause 14.3.2.

12. **CONFIDENTIALITY**

- 12.1 During the term of this Agreement and for a period of ten (10) years after its termination, each party (the "**Receiving Party**") agrees with the other (the "**Disclosing Party**"):
  - 12.1.1 to keep the Disclosing Party's Confidential Information confidential;
  - 12.1.2 not to access or use the Disclosing Party's Confidential Information except for performance of each SoW and acceptance of any deliverables;
  - 12.1.3 not to disclose the Disclosing Party's Confidential Information to a third party other than on a need-to-know basis to the Receiving Party's:

- (a) Affiliates;
- (b) officers and employees and those of its Affiliates that need to know the Confidential Information for the purpose of performing its obligations under this Agreement;
- (c) contractors and sub-contractors, professional advisers, consultants and agents and those of its Affiliates who are engaged to advise that party in connection with the Program or this Agreement; and
- (d) any other person to whom the Disclosing Party agrees in writing that Confidential Information may be disclosed in connection with the Program,

the “**Authorized Third Parties**”. The Authorized Third Parties shall be bound by obligations of confidentiality to the Receiving Party at least as stringent as those set forth herein.

12.2 The Receiving Party shall ensure that each of the Authorized Third Parties complies with obligations of confidentiality and nonuse no less restrictive than those specified hereunder with respect to the Disclosing Party's Confidential Information and shall remain primarily liable to the Disclosing Party for any act or omission of any of the Authorized Third Parties.

12.3 The Receiving Party shall within 30 (thirty) days of receipt of the Disclosing Party's written request (including after termination of this Agreement and any SoW):

- 12.3.1 deliver up to the Disclosing Party all items and copies of all or any Confidential Information of the Disclosing Party;
- 12.3.2 expunge and/or make irretrievable all Confidential Information of the Disclosing Party from any computer or other similar device in which it is stored and, if further requested, certify in writing signed by an authorized representative that it has done the same (provided that this clause 12.3.2 shall not apply to automatically archived electronic files or electronic back-ups made in the ordinary course of business, on secured central servers, which cannot reasonably be deleted and such electronic files shall be retained subject to the obligations of confidence set out in this clause 12); and
- 12.3.3 destroy all hard copies of notes, analyses or memoranda containing the Disclosing Party's Confidential Information (and, if further requested, certify in writing signed by an authorized representative that it has done the same)

provided that the Receiving Party shall be entitled to retain copies of the Confidential Information to enable it to monitor its obligations under this Agreement or which is required to be maintained by Applicable Laws or a Regulatory Authority subject always to the obligations of confidence under this Agreement.

12.4 Confidential Information shall not include information which:

- 12.4.1 is, or becomes, generally available to the public other than as a direct or indirect result of the information being disclosed by the Receiving Party or its Authorized Third Parties in breach of this Agreement (except that any compilation of otherwise public information in a form not publicly known shall still be treated as Confidential Information);
- 12.4.2 was available to the Receiving Party on a non-confidential basis prior to disclosure by the Disclosing Party, as evidenced by the Receiving Party's written records;

- 12.4.3 was, is, or becomes available to the Receiving Party on a non-confidential basis from a person who, to the Receiving Party's knowledge, is not under any confidentiality obligation in respect of that information;
- 12.4.4 was lawfully in the possession of the Receiving Party before the information was disclosed by the Disclosing Party, as evidenced by the Receiving Party's written records;
- 12.4.5 is developed by or for the Receiving Party independently of and without use of or reliance upon the information disclosed by the Disclosing Party, as evidenced by the Receiving Party's written records;
- 12.4.6 is necessarily disclosed by the Receiving Party pursuant to a statutory or regulatory obligation, but then only to the extent of such required disclosure and save that the Receiving Party shall, to the extent it is lawful to do so, give prompt prior notice to the Disclosing Party of any such potential disclosure and allow the Disclosing Party a reasonable opportunity to limit such disclosure; or
- 12.4.7 the Disclosing Party and the Receiving Party agree in writing is not confidential.

**12.5 NOTWITHSTANDING ANYTHING TO THE CONTRARY IN THIS AGREEMENT, EITHER PARTY MAY DISCLOSE THE EXISTENCE, TERMS AND CONDITIONS OF THIS AGREEMENT IN AN ELECTRONIC DATA ROOM TO PROSPECTIVE INVESTORS OR PARTNERS, PROVIDED THAT (A) ANY SUCH PARTY TO WHOM DISCLOSURE IS PERMITTED HAS AGREED IN WRITING TO KEEP SUCH INFORMATION CONFIDENTIAL, (B) ANY SUCH PARTY TO WHOM SUCH DISCLOSURE IS MADE IS NOT, IN THE CASE OF DISCLOSURE BY CUSTOMER, PRIMARILY A CONTRACT DEVELOPMENT AND/OR MANUFACTURING ORGANIZATION IN THE BIOPHARMACEUTICAL INDUSTRY, AND [\*] THE PARTY SHARING THE INFORMATION WITH ITS PROSPECTIVE INVESTORS OR PARTNERS SHALL REMAIN PRIMARILY LIABLE FOR ANY UNAUTHORIZED DISCLOSURE BY SUCH INVESTORS AND PARTNERS.**

**\*Confidential Treatment Requested.**

**13. CHANGE**

13.1 If a party wishes to change any aspect of this Agreement or any Scope of Work then the parties shall follow Fujifilm's standard change process (and such change shall be referred to as a "**Change**"). Upon determining that a modification to this Agreement or any Scope of Work is required, or requested by Customer, Fujifilm shall draft the Change and the Change will not be effective until signed by both Fujifilm and Customer.

**14. DELAY, CANCELLATION, TERMINATION AND CONSEQUENCES**

14.1 Delay:

- 14.1.1 If the Customer either causes or requests a material delay to any Stage; Stages; or the Program as a whole and that delay prevents, or will prevent, Fujifilm from performing a Stage or the Program as a whole in accordance with the Program Plan (a "**Delay**") and the parties cannot agree a Change to accommodate that Delay:
  - (a) then either the Batch Cancellation Fee(s) or the Program Cancellation Fee (as applicable) shall be payable; and
  - (a) the Batch Cancellation Fee or Program Cancellation Fee (as applicable) shall be calculated by reference to the date on which notice was given by the Customer in relation to the delay if such notice is given, or the date on which the delay becomes apparent to Fujifilm.
- 14.1.2 If the parties agree a Change to accommodate the Delay and that results in the Delayed Stage(s) or Program (as applicable) being performed partially within the

original period reserved for the Delayed Stage(s) or Program as a whole then the Batch Cancellation Fee(s) or the Program Cancellation Fee (as applicable) shall be reduced proportionally to reflect the period of time that the Program was Delayed (as determined by Fujifilm acting reasonably).

- 14.1.3 In the event that Fujifilm successfully books slots vacated by the Customer's Delay with a substantially equivalent program from a new customer or a substantially equivalent new program for an existing customer, the Customer shall not incur any Batch Cancellation Fee or Program Cancellation Fee (as applicable) associated with such manufacturing slot.

14.2 Termination of this Agreement as a whole

14.2.1 Fujifilm collectively or the Customer shall be entitled to terminate this Agreement (and all Scope of Works made under it) immediately upon giving notice to the other if:

- (a) the other party commits a material breach of clauses 8.4, 10, , 12, 19 and such breach:
  - (i) is not capable of remedy (a breach shall be considered capable of remedy if the party in breach can comply with the provision in question in all respects other than as to time of performance); or
  - (ii) is capable of remedy, and the breaching party fails to remedy the breach or (except for payment obligations) fails to commence remedy of the breach within sixty (60) days after receipt of notice giving full particulars of the breach and requiring it to be remedied, provided, however, that such cure period shall be suspended during any time that a party seeks resolution of a dispute as to whether an alleged material breach occurred pursuant to clause 16;
- (b) the other party takes any step or action in connection with its entering administration, provisional liquidation or any composition or arrangement with its creditors (other than in relation to a solvent restructuring), being wound up (whether voluntarily or by order of the court, unless for the purpose of a solvent restructuring), having a receiver appointed to any of its assets or ceasing to carry on business or, if the step or action is taken in another jurisdiction, in connection with any analogous procedure in the relevant jurisdiction; or
- (c) the other party or the person Controlling the other party has a change in Control and the new Controlling entity is reasonably considered by the party giving notice either to be its direct competitor or not to have reasonable financial creditworthiness; provided, however, that any acquirer of the Customer would only be considered a direct competitor to Fujifilm if such acquirer's primary business was contract manufacturing of biopharmaceuticals.

14.3 Termination of a Stage/Program by the Customer for Convenience

14.3.1 The Customer may cancel a Non-Manufacturing Stage for convenience by giving written notice to Fujifilm in which case:

- (a) the SoW shall terminate in respect of that Stage;
- (b) in all other respects the SoW shall continue in full force;

the Customer shall pay Fujifilm the Charges that are due for the Fujifilm Services that have been performed and [\*] of the Charges for the Fujifilm Services that have not yet been performed in that Non-Manufacturing Stage plus any Charges owed in respect of Ancillary Services that have been performed.

**\*Confidential Treatment Requested.**

- 14.3.2 The Customer may cancel any Manufacturing Stage for convenience by giving written notice to Fujifilm in which case:
  - (a) the SoW shall terminate in respect of that Stage;
  - (b) in all other respects the SoW shall continue in full force;
  - (c) the Customer shall pay the Charges that are due for the Fujifilm Services that have been performed and the relevant Batch Cancellation Fee plus any Charges owed in respect of Ancillary Services that have been performed.
- 14.3.3 The Customer may cancel a Program for convenience by giving written notice to Fujifilm in which case:
  - (a) the SoW(s) in respect of that Program shall terminate;
  - (b) the Customer shall pay the Charges that are due for the Fujifilm Services that have been performed and the Program Cancellation Fee plus any Charges owed in respect of Ancillary Services that have been performed.
- 14.3.4 If a critical Stage, or more than one Stage, under a Program is cancelled and that has the effect of cancelling a Program as a whole (as determined by Fujifilm acting reasonably) then clause 14.3.3 shall apply instead of clauses 14.3.1 and/or 14.3.2.

14.4 Termination by Fujifilm for an Unforeseen Technical Factor

- 14.4.1 If an Unforeseen Technical Factor occurs, and the parties are unable to agree to a Change to accommodate that Unforeseen Technical Factor, Fujifilm may terminate any affected Program without any liability to Customer by giving prior written notice to the Customer if Fujifilm reasonably believes that it will be unable to carry out and complete such Program in accordance with the Scope of Work due to the Unforeseen Technical Factor.
- 14.4.2 [\*]

14.5 Termination of a Scope of Work for Breach

- 14.5.1 If any party commits a material breach of a Scope of Work, the non-breaching party may give written notice to the other party, specifying the nature of the material breach and, if such material breach is not remedied within sixty (60) days or (other than payment obligations) a remedy is not commenced within sixty (60) days after receipt of such notice (provided, however, that the cure period shall be suspended during any time that a party seeks resolution of a dispute as to whether an alleged material

breach occurred pursuant to clause 16), then the non-breaching party shall have the right, in its sole discretion, to immediately terminate that Scope of Work.

14.5.2 If Fujifilm terminates a Scope of Work under this clause 14.5 or all Scopes of Work under clause 14.2 then, without prejudice to Fujifilm's other rights and remedies, the Program Cancellation Fee shall be payable by the Customer to Fujifilm plus any Charges owed in respect of Ancillary Services that have been performed.

14.6 If a party exercises any of its rights of termination in respect of only one or more SoWs then:

14.6.1 this Agreement shall terminate in respect of those SoWs and the provisions of this Agreement relating to termination of this Agreement shall apply in relation to those SoWs; and

14.6.2 in all other respects this Agreement shall continue in full force and those SoWs in respect of which the party has terminated this Agreement will be deemed to be removed from the definition of the SoWs.

14.7 Additional Consequences of Termination

14.7.1 Upon receipt of a notice of termination, Fujifilm shall make prompt, reasonable efforts to limit or terminate all outstanding costs and expenses related to provision of the Services and/or manufacture of the Product.

14.7.2 The termination of this Agreement or any Scope of Work shall be without prejudice to the rights and remedies of any party which may have accrued up to the date of termination.

14.7.3 On termination of this Agreement or any SoW (as applicable) for any reason whatsoever:

(a) Fujifilm shall provide all Materials and Results (in .pdf format) to Customer except as Fujifilm is required to retain under Applicable Laws, and Customer shall reimburse Fujifilm for associated reasonable, documented costs;

(b) save as set out in clause 10 the relationship of the parties shall cease and any rights or licenses granted under or pursuant to this Agreement shall cease to have effect save as (and to the extent) expressly provided for in this clause 14;

(c) the provisions of the following clauses together with any provision which expressly or by implication is intended to come into or remain in force on or after termination shall continue in full force and effect clauses 1, 4.3, 8, 9, 10, 11, 129, 14, 16, 18, and 22; and

[\*]

**\*Confidential Treatment Requested.**

15. **FORCE MAJEURE**

15.1 Subject to clause 15.2, no party shall be liable to the other(s) for any delay or non-performance of its obligations under any Scope of Work (except for the payment of money) arising from a Force Majeure Event.

15.2 If a party is delayed or prevented from performing its obligations due to a Force Majeure Event such party shall:

- 15.2.1 give notice of such Force Majeure Event to the non-affected parties as soon as reasonably practical stating the commencement date and extent of such delay or prevention, the cause thereof and its estimated duration;
- 15.2.2 use reasonable endeavors to mitigate the effects of such Force Majeure Event; and
- 15.2.3 resume performance of its obligations as soon as reasonably practicable.

15.3 If the Force Majeure Event in question continues for more than 3 (three) months any party to the affected Scope of Work may give notice in writing to the other(s) to terminate that Scope of Work. The notice to terminate must specify the termination date, which must not be less than ten (10) Business Days after the date on which the notice is given, and once such notice has been validly given, that Scope of Work will terminate on that termination date.

16. **DISPUTE RESOLUTION**

16.1 If there is a dispute in relation to or in connection with the QA Documents, such dispute shall be dealt with in accordance with the procedures set out in the Quality Agreement.

16.2 In respect of any dispute concerning this Agreement (other than a dispute in connection with the QA Documents) the parties shall seek to resolve the matter as follows:

- 16.2.1 by referral in writing summarizing the nature of the dispute by a party in the first instance to the decision of each party's Program Manager;
- 16.2.2 if the dispute is not resolved within 10 (ten) Business Days of its referral to the Program Managers it shall be referred to the decision of Fujifilm's SVP of Program Management and the Customer's President or Chief Executive Officer; and
- 16.2.3 if the dispute is not resolved within 10 (ten) Business Days of its referral to Fujifilm's SVP of Program Management and the Customer's President or Chief Executive Officer it shall be referred to the decision of each party's President or Chief Executive Officer (as applicable/appropriate).

16.3 Binding Arbitration. Except with respect to any matters involving confidentiality and/or intellectual property, if the dispute between the parties is not resolved having applied the process set out at clause 16.2 then the dispute shall be settled solely and exclusively by arbitration in accordance with the Comprehensive Arbitration Rules and Procedures of JAMS, upon application of either party. Unless otherwise agreed by the parties, the arbitration shall be conducted New York City, NY. before a panel of three arbitrators each of whom is experienced and knowledgeable in the pharmaceutical manufacturing industry, and at least one of the arbitrators will be an attorney. One arbitrator will be appointed by each party to serve on the panel. One neutral arbitrator will be appointed by the two arbitrators. If the two arbitrators selected cannot agree on the appointment of the third arbitrator within twenty (20) days of their appointment, or if either party shall fail to appoint its arbitrator within twenty (20) days after receipt of notice of demand for arbitration, such arbitrator(s) not appointed shall be selected and appointed by JAMS upon application of either party. The costs and expenses of each arbitration hereunder and their apportionment between the parties will be determined by the arbitrators in their award or decision. Judgment upon any award of the majority of the arbitrators shall be final, binding and conclusive, and may be entered upon the motion of either party in a court of competent jurisdiction.

16.4 Notwithstanding the provisions of this clause 16 any party may commence or take proceedings or seek remedies before the courts or any other competent authority for interim, interlocutory, injunctive or other equitable remedies in relation to this Agreement.

17. **AUDIT**

17.1 The Customer may carry out audits at the times, and in accordance with the terms, set out in the Quality Agreement provided that access by the Customer and/or its representatives to

records, information and systems shall be on a supervised basis, subject to the Customer complying with the security and confidentiality requirements of Fujifilm to protect information which relates to anything other than the Programs and shall be limited to those days as stated in the Quality Agreement

17.2 Audit access shall not be extended to Fujifilm's confidential records, including details of financial transactions and contracts with third parties that relate to this Agreement.

17.3 If Fujifilm is in material breach of this Agreement or if the Customer reasonably believes that Fujifilm is in material breach of this Agreement, the Customer may upon giving reasonable written notice to Fujifilm carry out an audit on the same basis as in clauses 17.1 and 17.2.

17.4 Additional audits (other than those carried out pursuant to clause 17.1 and 17.2) may be carried out on the same basis as in clauses 17.1 and 17.2 subject to (i) payment of Fujifilm's costs and expenses and the agreement of a commercial rate; and (ii) the Customer ensuring such audit will not delay or disrupt Fujifilm's operations at the Facility.

18. **NOTICES**

18.1 Subject to clause 18.2 the parties may communicate with each other in any way that is normal in the course of their business.

18.2 Any notice given under clauses 3, 8, 9, 11, 12, 14, 15, 16, 17, 18.2, 19 or 20 shall only be effective if it is in writing, sent to a party at its address or email address and for the attention of the individual, as set out in Schedule 2 (or such other address, email address or individual as that party may notify the other in accordance with this clause 18) and is given in accordance with clauses 18.3 to 18.5 below.

18.3 Where a notice must be given to Fujifilm under clauses 3.2, 14 or 20.2 such notice must be given to FBDK, FBDT and FDBU.

18.4 Notice may be given by hand or sent by email (with confirmation by another form of notice provided hereunder), recorded delivery, registered post or airmail and will be deemed to have been duly served:

18.4.1 if delivered by hand, at the time and date of delivery;

18.4.2 if sent by email, at the time and date of sending;

18.4.3 if sent by recorded delivery or registered post, 48 (forty eight) hours from the date of posting (such date as evidenced by postal receipt); and

18.4.4 if sent by registered airmail, five days from the date of posting,

provided that, where in the case of delivery by hand or transmission by email, such delivery or transmission occurs either after 4.00pm on a Business Day, or on a day other than a Business Day, service will be deemed to occur at 9.00am on the next Business Day.

18.5 In proving service of a notice it will be sufficient to prove that delivery was made or that the envelope containing the notice or document was properly addressed and posted (either by prepaid first class recorded delivery post or by prepaid airmail, as the case may be) or that no failed delivery message was received, as the case may be.

19. **EXPORT CONTROLS, MODERN SLAVERY AND CORRUPTION**

19.1 The Customer acknowledges that export and/or use of any Product may be subject to compliance with laws, rules and regulations of bodies having jurisdiction over such operations.

If the export or use of any Products is so controlled, it is the responsibility of the Customer to obtain any such approval required by any applicable laws, rules or regulations.

19.2 Each party shall endeavour to hold itself and its suppliers to the highest performance, ethical and compliance standards, including basic human rights, not engaging in any activity, practice or conduct which would constitute an offence under anti-slavery legislation in the United Kingdom or the U.S.A, encouraging fair and equal treatment for all persons, the provision of safe and healthy working conditions, respect for the environment, the adoption of appropriate management systems and the conduct of business in an ethical manner. In performing its duties under this Agreement, each party acknowledges the value and importance of performance and ethical behaviour in its performance under this Agreement.

19.3 Each party warrants that on the Effective Date and each SoW Effective Date, it, its directors, officers or employees have not offered, promised, given, authorized, solicited or accepted any undue pecuniary or other advantage of any kind (or implied that they will or might do any such thing at any time in the future) in any way connected with this Agreement or a SoW and that it has taken reasonable measures to prevent subcontractors, agents or other third parties, subject to its control or determining influence, from doing so.

19.4 The parties agree that, at all times in connection with and throughout the term of this Agreement, they will comply with and that they will take reasonable measures to ensure that their subcontractors, agents or other third parties will comply with all applicable anti-corruption legislation including the Bribery Act 2010 or the Foreign Corrupt Practices Act 1977.

19.5 Each party shall not do, or omit to do, any act that would cause one of the other parties to be in breach of any anti-corruption legislation including the Bribery Act 2010 or the Foreign Corrupt Practices Act 1977.

20. **ASSIGNMENT AND SUB-CONTRACTING**

20.1 A party may assign or transfer all of its rights and responsibilities under this Agreement to:

20.1.1 an Affiliate provided that such Affiliate has reasonable financial creditworthiness; or

20.1.2 a purchaser of all or substantially all of the equity of the assigning party provided that such third party has reasonable financial creditworthiness; or

20.1.3 a purchaser of all or substantially all of assets to which this Agreement relates provided that such third party has reasonable financial creditworthiness,

but not otherwise without written consent of the other parties (such consent not to be unreasonably withheld or delayed) and provided that (a) the assignee agrees in writing to assume all obligations undertaken by its assignor in this Agreement and (b) in relation to assignment in part no such assignment shall relieve the assigning party of responsibility for the performance of any of its obligations under this Agreement.

20.2 If a party assigns or transfers all or any of its rights and responsibilities under clause 20.1 it shall promptly notify the other parties in writing.

20.3 Fujifilm may sub-contract all or any of its obligations under this Agreement provided that in relation to any subcontracting of any activities that involve manufacture, processing, handling, analytical testing of Product, storage of Product, or any other cGMP activities contracted by the parties relating to the Product, Fujifilm will obtain the Customer's prior written consent (which may be by signature of the relevant SoW(s) which specify that an obligation will be sub-contracted). By way of clarity, Fujifilm shall not be obligated to obtain Customer's prior consent for subcontracting services related to facility maintenance, cleaning, equipment validation, raw material testing and similar services.

20.4 The appointment of any subcontractor shall not relieve the party sub-contracting from any liability or obligation under this Agreement and the party sub-contracting shall be responsible

for all acts and omissions of the subcontractor to the same extent as if they were its own acts or omissions.

21. **GENERAL**

- 21.1 **Entire agreement:** This Agreement contains all the terms which the parties have agreed with respect to the subject matter herein and supersedes all previous agreements and understandings between the parties (whether oral or in writing) relating to such subject matter. Each party acknowledges and agrees that it has not been induced to enter into this Agreement by a statement or promise which it does not contain. Each party confirms that save as otherwise expressly set out in this Agreement, the other party gives no warranties either in this Agreement or elsewhere in connection with the provision of the Programs. Nothing in this clause 21.1 shall exclude or limit a party's liability for fraud, including fraudulent misrepresentation.
- 21.2 **Third party rights:** Save as expressly set out in this Agreement, the parties do not intend that any person who is not a party to this Agreement shall have any right to enjoy the benefit or enforce any of the terms of this Agreement.
- 21.3 **Amendments:** With the exception of Changes, which shall be subject to clause 0, no amendment to this Agreement shall be valid unless in writing and signed by a duly authorized representative of each of the parties. A party is entitled to assume that a representative of another party is authorized to act on that party's behalf if that individual is apparently or seemingly acting in the normal course of the business relationship. An exchange of emails shall not be capable of constituting an agreement to amend this Agreement.
- 21.4 **Waiver:** No failure or delay by a party to exercise any right or remedy provided under this Agreement or by law shall constitute a waiver of that or any other right or remedy, nor shall it preclude or restrict the further exercise of that or any other right or remedy. The single or partial exercise by any party of any right, power or remedy under this Agreement shall not in any circumstances preclude any other or further exercise of it, or the exercise of any right, power or remedy. A waiver by any party of a breach of any provision of this Agreement shall not be considered as a waiver of a subsequent breach of the same or any other provision of this Agreement.
- 21.5 **Severability:** If any provision of this Agreement or a SoW is found by any court or administrative body of competent jurisdiction to be invalid, illegal or unenforceable in any jurisdiction then it shall be deemed modified to the minimum extent necessary to make it valid, legal and enforceable. If such modification is not possible that provision shall be deemed to be omitted from this Agreement or the SoW in so far as this Agreement or that SoW relates to that jurisdiction and the validity and enforceability of that provision in other jurisdictions and the other provisions of this Agreement or SoW shall not be affected or impaired.
- 21.6 **Counterparts:** This Agreement may be executed in any number of counterparts. Any party may enter into this Agreement by executing a counterpart and all the counterparts taken together will constitute one and the same agreement. This Agreement shall not be effective until each party has signed one counterpart.
- 21.7 **Publicity:** The parties agree that, except as necessary to comply with Applicable Laws, no party shall make any official press release, public announcement or other formal publicity relating to the transactions which are the subject of this Agreement, without first obtaining in each case the prior written consent of the other parties, which consent shall not be unreasonably withheld. If a party is required under any securities laws or regulations to disclose the terms of this Agreement (in summary, in whole or in part), such party shall provide a redacted version of the disclosure to the other party and give such other party adequate time to review and propose further redactions. The parties shall work in good faith to redact confidential and proprietary information of each party prior to such required disclosure.
- 21.8 **Independent Contractors:** Nothing in this Agreement shall create, or be deemed to create, a partnership or the relationship of principal and agent or employer and employee between the

parties. Each party agrees to perform under this Agreement solely as an independent contractor.

21.9 Duty to Mitigate: Each of the parties shall use all reasonable endeavors to mitigate any costs, losses or expenses due to be incurred or suffered by the other party in connection with the performance or non-performance of this Agreement.

22. **GOVERNING LAW**

22.1 The formation, existence, construction, performance, validity and all aspects whatsoever of this Agreement (including any Scope of Work) or any term of it and any issues, disputes or claims arising out of or in connection with it (whether contractual or non-contractual in nature) shall be governed by, and construed in accordance with, the State of Delaware, without regard to conflicts of law provisions. Subject to clause 16, the parties hereby submit to the jurisdiction of the Delaware courts, both state and federal, in all matters concerning this Agreement.

**IN WITNESS** of the above the parties have signed this Agreement on the date of last signature below.

**Schedule 1****Charges**

In addition to the Charges for the Fujifilm Services (as the same are described in the relevant Scope of Work); the Customer will pay to Fujifilm Charges in consideration of the 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 (the "**Ancillary Services**") as calculated in accordance with this Schedule 1.

**1. Charges for Consumables in Non-Manufacturing Stage and Manufacturing Stage**

At the time set out in the Scope of Work, or in the course of the Program as mutually agreed in writing by the parties, the Customer shall pay to Fujifilm an amount in advance in consideration of the Ancillary Services relating to the purchase of Consumables intended to be used during the applicable Non-Manufacturing Stages and Manufacturing Stages. This will be an amount based upon an estimation of the sums required to purchase Consumables based upon Fujifilm's historical data from previous manufactures at the applicable scale of production plus [\*] of such sums [\*], (the "**Consumables Advance Payment**").

**\*Confidential Treatment Requested.**

1.2 On completion of each Non-Manufacturing Stage or Manufacturing Stage, Fujifilm shall calculate the expenditure incurred in respect of Consumables procured for use during such Non-Manufacturing Stage or Manufacturing Stage and shall add a sum equivalent to [\*] of all such expenditure on to such sum [\*], the aggregate amount being referred to as "**Actual Production Expenditure**".

1.3 If the Actual Production Expenditure is greater than the Consumables Advance Payment, Fujifilm shall issue a further invoice for the Ancillary Services in relation to the Consumables for a sum equivalent to the difference. If the Actual Production Expenditure is less than the Consumables Advance Payment, Fujifilm shall issue a credit note against the earlier invoice for a sum equivalent to the difference to be applied to the Charges for the following Stage (if there is one).

1.4 Each month, Fujifilm shall issue an invoice to the Customer in relation to the Ancillary Services regarding any Consumables used during any Stage during the previous month in amounts which are not covered in paragraphs 1.2 and 1.3 above equivalent to the expenditure on such additional Consumables during the previous month plus an amount equal to [\*] of such expenditure.

**2. Additional Charges in Respect of Subcontracted Work, Process-Specific Equipment, Modifications and Special Waste**

2.1 Fujifilm shall obtain the Customer's approval in writing prior to incurring expenditure on Ancillary Services relating to Subcontracted Work, Process-Specific Equipment, Modifications and disposal of Special Waste.

2.2 If approved by the Customer under paragraph 2.1, Fujifilm shall bear such expenditure itself.

2.3 Fujifilm shall invoice the Customer for the Ancillary Services relating to the Subcontracted Work, Process-Specific Equipment, Modifications and disposal of Special Waste as the case may be in the same amount as the expenditure which Fujifilm incurs in respect of such Ancillary Services plus a sum equivalent to [\*] of such expenditure.

2.4 Fujifilm shall issue invoices for such Ancillary Services either at the time Fujifilm incurs expenditure in respect of the Subcontracted Work, Process-Specific Equipment, Modifications and/or disposal of Special Waste or as set out in the relevant SoW as the case may be.

**3. Purchase of Process-Specific Consumables and Process-Specific Equipment by the Customer on completion of the relevant Stage or termination**

Subject to clause 10.3 and the payment of all relevant Charges, the Customer shall have an option to purchase from Fujifilm such Process-Specific Equipment and/or Process-Specific Consumables purchased by Fujifilm under paragraphs 1 and 2 of this Schedule 1 as remain following completion of the relevant Stage for which such Process-Specific Equipment and/or Process-Specific Consumables were purchased for consideration of [\*] payable, if the work is performed in the UK or USA respectively, at the time of such sale.

**\*Confidential Treatment Requested.**

3.2 The option in paragraph 3.1 shall be exercised within 2 (two) months following completion of the relevant Stage under which such Process-Specific Equipment and/or Process-Specific Consumables were purchased or termination of this Agreement, (whichever occurs first).

3.3 The Customer shall be responsible for any cost and expense associated with removal/delivery of such Process-Specific Equipment and/or Process-Specific Consumables and documenting such sale. Such Process-Specific Equipment and/or Process-Specific Consumables shall be delivered Ex Works the Facility (Incoterms 2010). Risk in and title to such Process-Specific Equipment and/or Process-Specific Consumables shall pass on delivery.

3.4 Upon [\*] prior written notice to the Customer, Fujifilm shall be free to use or destroy (at the Customer's cost) any item(s) of Process-Specific Equipment or Process-Specific Consumables in respect of which the option referred to in this paragraph 333 is not exercised or for which their assigned expiry date has passed.

**4. Product Samples, Cell Banks and other materials on completion or termination**

4.1 Prior to completion of each Program, the Customer shall notify Fujifilm what (if any) samples and/or cell banks used during the Program the Customer wishes Fujifilm to deliver to the Customer and, subject to clause 10.3, delivery of those samples/cell banks shall take place in accordance with clause 7. If the Customer does not give any such notification to Fujifilm prior to completion of the Program, Fujifilm may destroy such samples and/or cell banks at the Customer's cost upon thirty (30) days' prior written notice to the Customer.

4.2 Upon [\*] prior written notice to the Customer, Fujifilm shall be entitled, in a manner of its choosing and without further notice to the Customer, to dispose of any Product, samples, cell banks or other property of the Customer which remains in the possession of Fujifilm in [\*] following the effective date of termination.

**5. Batch Cancellation Fees**

5.1 The Batch Cancellation Fee shall be:

5.1.1 the applicable [\*] and associated Disposition Fees (detailed in the SoW) set out in the table below, which will reflect the [\*] between:

- (a) notice of cancellation of such Batch(es); and
- (b) the then current date for [\*];

5.1.2 less any sums already received under the SoW for the Fujifilm Services in relation to the cancelled Batch(es) that have not been performed at the time the Batch Cancellation Fee is calculated.

5.2 [\*] payable:

[*]	[*]
[*]	[*]

[*]	[*]
[*]	[*]

**\*Confidential Treatment Requested.**

**6. Program Cancellation Fees**

6.1 The Program Cancellation Fee shall be:

6.1.1 the applicable [\*] (detailed in the SoW(s)) that is being cancelled set out in the table below, which will reflect the [\*] between:

- (a) notice of cancellation of the Program; and
- (b) the then current date for [\*]

6.1.2 less any sums already received under the SoW(s) for the Fujifilm Services in relation to the cancelled element of the Program that have not been performed at the time the program Cancellation Fee is calculated.

6.2 [\*] payable:

[*]	[*]
[*]	[*]
[*]	[*]
[*]	[*]

Schedule 2

Addresses for Notice

<p><b>FDBK:</b></p> <p>Contact: Chief Operating Officer</p> <p>Address: FUJIFILM Diosynth Biotechnologies UK Limited, Belasis Avenue, Billingham, TS23 1LH</p> <p>Nominated email address:</p>	<p><b>Copied to:</b></p> <p>Contact: Legal Counsel</p> <p>Address: Fujifilm Diosynth Biotechnologies, Belasis Avenue, Billingham, TS23 1LH, England</p> <p>Nominated email address: fdbklegal@fujifilm.com</p>
<p><b>FDBT:</b></p> <p>Contact: Chief Operating Officer</p> <p>Address: FUJIFILM Diosynth Biotechnologies Texas, LLC 100 Discovery Drive, Suite 200 College Station, Texas, 77845</p> <p>Nominated email address:</p>	<p><b>Copied to:</b></p> <p>Contact: Legal Department</p> <p>Address: FUJIFILM Holdings America Corporation, 200 Summit Lake Drive, Valhalla, NY 10595.</p> <p>Nominated email address: legaldepartment@fujifilm.com</p>
<p><b>FDBU:</b></p> <p>Contact: President</p> <p>Address: FUJIFILM Diosynth Biotechnologies U.S.A., Inc. 101 J. Morris Commons Lane, Morrisville, NC 27560</p> <p>Nominated email address:</p>	<p><b>Copied to:</b></p> <p>Contact: Legal Department</p> <p>Address: FUJIFILM Holdings America Corporation, 200 Summit Lake Drive, Valhalla, NY 10595.</p> <p>Nominated email address: legaldepartment@fujifilm.com</p>
<p><b>Customer:</b></p> <p>Contact:</p> <p>Address:</p> <p>Nominated email address:</p>	<p>President &amp; Chief Executive Officer</p> <p>Aeglea BioTherapeutics, Inc., 901 S. Mopac Expressway, Barton Oaks Plaza One, Suite 250, Austin, TX 78746</p>

**Signature Page**

**SIGNED** for and on behalf of **FUJIFILM DIOSYNTH BIOTECHNOLOGIES TEXAS, LLC:**

**Signature:/s/ Gerry Farrell  
GERRY FARRELL**

**Title: COO**

**Date: 11 NOV 18**

**Signature:**

**Title: N/A /s/ GF**

**Date: 11/11/18**

**SIGNED** for and on behalf of **FUJIFILM DIOSYNTH BIOTECHNOLOGIES U.S.A., INC:**

**Signature:/s/ Andy Fenny  
A FENNY**

**Title: C.B.O**

**Date: 07 NOV 18**

**Signature:**

**Title: N/A /s/ Andy Fenny**

**Date:**

**SIGNED** for and on behalf of **FUJIFILM DIOSYNTH BIOTECHNOLOGIES UK LIMITED:**

**Signature:/s/ Paul Found  
PAUL FOUND**

**Title: COO**

**Date: 12 NOV 2018**

**SIGNED** for and on behalf of **AEGLEA BIOTHERAPEUTICS, INC.:**

**Signature: /s/ Leslie Sloan**

**Signature: /s/ Charles York**

**Title: SVP, Operations**

**Title: CFO**

**Date: 11-26-18**

**Date: 26-nov-2018**

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-217573 and 333-228967) and Form S-8 (No. 333-210633, 333-216903, and 333-223614) of Aeglea BioTherapeutics, Inc. of our report dated March 7, 2019 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP  
Austin, Texas  
March 7, 2019

**Certification of Periodic Report under Section 302 of the Sarbanes-Oxley Act of 2002**

I, Anthony G. Quinn, M.B. Ch.B. Ph.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Aeglea BioTherapeutics, Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
  - a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
  - b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
  - c. Evaluated the effectiveness of the registrant's disclosure controls and procedures, and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
  - d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
  - a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
  - b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 7, 2019

/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)*

**Certification of Periodic Report under Section 302 of the Sarbanes-Oxley Act of 2002**

I, Charles N. York II, certify that:

1. I have reviewed this Annual Report on Form 10-K of Aeglea BioTherapeutics, Inc;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
  - a. Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
  - b. Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
  - c. Evaluated the effectiveness of the registrant's disclosure controls and procedures, and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
  - d. Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
  - a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
  - b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 7, 2019

/s/ Charles N. York II  
Charles N. York II  
*Chief Financial Officer and Vice President (Principal  
Accounting Officer and Principal Financial Officer)*

**Certification Of  
Principal Executive Officer  
Pursuant To 18 U.S.C. Section 1350,  
As Adopted Pursuant To  
Section 906 of The Sarbanes-Oxley Act Of 2002**

In connection with the Annual Report of Aeglea BioTherapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Anthony G. Quinn, M.B. Ch.B. Ph.D., President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

- 1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- 2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: March 7, 2019

/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)*

**Certification Of  
Principal Financial Officer  
Pursuant To 18 U.S.C. Section 1350,  
As Adopted Pursuant To  
Section 906 Of The Sarbanes-Oxley Act Of 2002**

In connection with the Annual Report of Aeglea BioTherapeutics, Inc. (the "Company") on Form 10-K for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Charles N. York II, Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

- 1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- 2) The information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Dated: March 7, 2019

/s/ Charles N. York II

Charles N. York II

*Chief Financial Officer and Vice President*

*(Principal Financial Officer and Principal Accounting Officer)*