

Aeglea BioTherapeutics, Inc.  
Form 10-K  
March 23, 2017

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, 2016

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                                 | 46-4312787          |
| (State or Other Jurisdiction of          | (I.R.S. Employer    |
| Incorporation or Organization)           | Identification No.) |
| 901 S. MoPac Expressway                  |                     |
| Barton Oaks Plaza One                    |                     |
| Suite 250                                |                     |
| Austin, TX                               | 78746               |
| (Address of Principal Executive Offices) | (Zip Code)          |

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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<br><br>(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 and posted on its corporate website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

Indicate by check mark if disclosure of delinquent filers pursuant to 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 or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "Smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one)

Large accelerated filer  Accelerated filer

Non-accelerated filer  Smaller reporting company

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, 2016 (the last business day of the Registrant's second fiscal quarter), based upon the closing price of \$4.86 of the Registrant's common stock as reported on the NASDAQ Global Market, was approximately \$24.6 million.

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

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| Class                                      | Outstanding at March 23, 2017 |
|--|-------------------------------|
| Common stock, \$0.0001 par value per share | 13,452,260 shares             |

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2017 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2016 fiscal year and is incorporated by reference into Part III of this Report.

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SPECIAL NOTE REGARDING 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 clinical development activities, expected results of clinical trials, future results of operations and financial position, our business strategy and plans and our objectives for future operations, are forward-looking statements. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “aim,” “anticipate,” “intend,” “could,” “would,” “project,” “plan” “expect,” and similar expressions that convey uncertainty of events or outcomes are intended to identify forward-looking statements.

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

## PART I

### ITEM 1. BUSINESS

#### Overview

We are a biotechnology company committed to developing enzyme-based therapeutics in the field of amino acid metabolism to treat rare genetic diseases and cancer. Our engineered human enzymes are designed to degrade specific amino acids in the blood to target these diseases. In inborn errors of metabolism, or IEM, a subset of rare genetic diseases, we are seeking to reduce the toxic levels of amino acids in patients to the normal range. In oncology, we are seeking to reduce amino acid blood levels below the normal range where we believe we will be able to exploit the dependence of certain cancers on specific amino acids.

Our lead product candidate, AEB1102 (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 I deficiency, an IEM, as well as some cancers which have been shown to have a metabolic dependence on arginine. AEB1102 has demonstrated clinical proof of mechanism in both scenarios. In a Phase 1 clinical trial for the treatment of patients with Arginase I deficiency, a dose-proportional reduction in plasma arginine levels was observed in two patients. A reduction in blood arginine levels was also observed in Phase 1 clinical trials for the treatment of patients with advanced solid tumors and the hematological malignancies relapsed refractory acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS. These preliminary results support its potential use as a therapeutic of both Arginase I deficiency and certain cancers associated with abnormal amino acid metabolism.

We are conducting three clinical trials for AEB1102, consisting of one Phase 1/2 clinical trial for the treatment of Arginase I deficiency and two Phase 1 clinical trials for the treatment of certain cancers.

•**Arginase I Deficiency.** Following completion of dosing for the first two adult patients in our Phase 1 clinical trial for the treatment of patients with Arginase I deficiency, we submitted a protocol amendment in November 2016 to broaden the scope of our Phase 1 trial into a Phase 1/2 trial. The amended protocol includes dosing of pediatric patients (two and older) and weekly repeat dosing, with the intent to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical response of AEB1102 in patients with this IEM. In the first quarter of 2017, we received IRB approval for the Phase 1/2 protocol for the treatment of patients with Arginase I deficiency at multiple clinical trial sites. In March 2017, we received an information request from the FDA which included comments and recommendations on the protocol amendment and a request for supporting documents based on their review of our completed toxicology studies, our dose escalation plan and our information to support the inclusion of pediatric patients. As recommended by the FDA, we replied with supporting information and requested a follow-up meeting. At this time, we believe our Phase 1/2 protocol provides an appropriate path to evaluate the safety and tolerability of AEB1102 in pediatric patients, and pending FDA feedback, we plan to initiate dosing in pediatric patients in the middle of 2017. In March 2017, we announced results from the first two adult patients in our Phase 1 clinical trial for the treatment of Arginase I deficiency at the 2017 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, or ACMG Annual Meeting. We intend to continue enrollment of adult patients and plan to dose additional adult patients in the middle of 2017. Topline data from this trial is expected in the first half of 2018..

•**Advanced Solid Tumors.** In October 2015, we initiated enrollment for a Phase 1 dose escalation trial for cancer patients with advanced solid tumors. In this ongoing trial, patients have demonstrated a reduction in blood arginine levels from the dosing of AEB1102, providing proof-of-mechanism. We expect to announce results of this Phase 1 dose escalation in patients with advanced solid tumors and anticipate initiating expansion arms in specific solid tumor types, potentially in combination with existing or emerging standards of care, in the fourth quarter of 2017 or the first quarter of 2018.

**Hematological Malignancies.** In July 2016, we initiated a Phase 1 clinical trial in patients with the hematological malignancies AML and MDS in the United States and Canada. As demonstrated in the trial for patients with advanced solid tumors, the first three cohorts of this trial have demonstrated proof-of-mechanism. We expect to announce results of the Phase 1 dose escalation trial in patients with AML and MDS in the fourth quarter of 2017 or the first quarter of 2018.

Our pipeline of engineered human enzyme product candidates in preclinical development includes: AEB3103, an enzyme that degrades the amino acid cysteine, and its oxidized form cystine, to target a widely recognized, but previously

underexploited vulnerability of cancer to oxidative stress; AEB2109, an enzyme that degrades the amino acid methionine to target methionine-dependent cancers and AEB4104, an engineered human enzyme to treat another IEM by degrading the amino acid homocysteine. We plan to continue preclinical development of AEB3103, AEB2109, AEB4104 and related variants of these candidates with the aim of submitting an IND for one or more of these development candidates in 2018.

We are a patient-focused organization conscious of the fact that IEM and oncology patients have limited treatment options, and we recognize that their lives and well-being are highly dependent upon our efforts and the efforts of others to develop improved therapies. For this reason, we are passionate about discovering and developing therapeutics to address IEM and oncology indications where there is a significant unmet medical need. Our goal is to create a world-class company committed to efficiently developing a portfolio of product candidates to treat these diseases.

### Our Strategy

Our goal is to build a fully integrated biotechnology company dedicated to the development and commercialization of engineered human enzymes targeting abnormal metabolism to transform the lives of patients. To execute our strategy, we intend to:

- Successfully advance our lead product candidate, AEB1102, through clinical development.

For Arginase I deficiency, we have received orphan drug designation from the U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA, and Fast Track Designation from the FDA. We initiated a Phase 1/2 dose escalation trial in the United States to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical response of AEB1102. If the results from the trial are supportive, we anticipate initiating a Phase 3 registration directed trial in the United States in 2018. For our oncology indications, we are conducting Phase 1 trials in patients with advanced solid tumors and in patients with the hematological malignancies AML and MDS. We plan to initiate single agent expansion arms in patients with selected solid tumors and hematological malignancies. Additionally, we plan to initiate a Phase 1b/2 trial, potentially in combination with existing or emerging standards of care in one or more solid tumor types and hematological malignancies. If we see compelling evidence of anti-tumor activity in the expansion phase of our solid tumor or hematological malignancies clinical trials, we plan to meet with regulatory authorities to discuss expedited regulatory strategies such as Breakthrough Therapy and Fast Track designations.

- Target enzyme-based therapeutic opportunities within IEM and oncology that have a defined blood-based mechanism of action and known disease pathways.

Our focus is on those rare genetic diseases and cancers where we have a deep understanding of their biology and have proof-of-mechanism that our approach plays a crucial role in addressing unmet needs in cancer and rare genetic diseases. Our lead product candidate AEB1102 has shown proof-of-mechanism in degrading blood arginine levels in patients with Arginase I deficiency, advanced solid tumors, and the hematological malignancies AML and MDS. Similarly, the dependence of various cancers on arginine is well understood and documented in the scientific and medical literature. We believe that developing product candidates that directly impact known disease pathways will increase the probability of success of our development programs.



• 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 patients that will benefit most from amino acid depletion therapy. In the United States, we are working to optimize newborn screening methods to more accurately identify patients with Arginase I deficiency. In oncology, we are exploring the predictive value of candidate biomarkers to identify patients with tumors sensitive to amino acid deprivation. We believe that targeting these patients may lead to potential proof-of-concept earlier in clinical development and a greater chance of success of treating their cancers effectively. When necessary, we intend to facilitate the development of companion diagnostics with the help of technology partners to aid us in identifying patients whose tumors may be susceptible to amino acid depletion therapy.

• Concurrently develop and commercialize multiple product candidates.

Development of multiple engineered human enzyme therapeutics generates organizational efficiencies and economies of scale. As a result, we believe we can concurrently develop several clinical-stage product candidates, resulting in a more diversified portfolio that provides multiple opportunities to create value. In addition, we have built an internal team of research scientists to work independently in our own research laboratory to

leverage our relationships with the University of Texas at Austin and other academic institutions to expand our portfolio of product candidates. Similarly, our Clinical Operations and Medical Sciences teams have created a network of leading medical institutions eager to investigate our pipeline in future clinical trials.

Seek global approval and commercialization of our product candidates.

We retain worldwide intellectual property rights for all of our product candidates. We will pursue clinical and regulatory programs for approval in the United States and internationally. Our plan is to establish a focused commercial organization in the United States and strategically evaluate partnership opportunities internationally.

### Our Focus—Abnormal Amino Acid Metabolism

Our company was founded to develop therapeutics for diseases characterized by abnormal amino acid metabolism. Metabolism refers to fundamental chemical reactions that are critical to life-sustaining processes. Metabolism follows specific pathways that are comprised of various biochemical reactions generally catalyzed by proteins known as enzymes. Enzymes accelerate complex reactions and serve as key regulators of metabolic pathways by responding to changes in the cell's environment or signals from other cells.

An in-depth understanding of abnormal metabolic pathways is crucial to developing therapies that may address various disease states, including rare genetic diseases and cancer. Our core capability of exploiting the metabolic pathways of IEMs 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 inborn errors of metabolism

Enzymatic defects in metabolic processes contribute to a class of genetic diseases known as IEM. These are a broad group of hundreds of rare genetic diseases where the defect in a single metabolic enzyme disrupts the normal functioning of a metabolic pathway. These defects lead either to abnormal accumulation of upstream metabolites that may be toxic or interfere with normal function, or to a reduced ability to synthesize essential downstream metabolites.

Most of these diseases often have severe or life-threatening characteristics. The incidence of a single IEM often occurs in fewer than one per 100,000 live births. Many IEMs are likely to be under-diagnosed. Current treatment options for many of these disorders are limited. Diet modification or nutrient supplementation can be beneficial in some IEMs. Several of these disorders have been treated successfully with enzyme therapy. We are targeting a urea cycle disorder, Arginase I deficiency, for our lead product candidate, AEB1102. This cycle has the principle function of detoxifying ammonia, a normal byproduct of amino acid metabolism. Arginase I reduces arginine levels, and is the final step of the urea cycle, releasing urea for secretion by the kidney. While a protein restricted diet is part of the treatment regimen for Arginase I deficiency, it is not effective in normalizing blood arginine due to the body's continued production and processing of ammonia that results in continued production of arginine. Symptoms resulting from defects in the urea cycle metabolic pathway, such as hyperammonemic encephalopathy, have been the successful target of other drug development efforts including RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylacetate) which help to remove ammonia. Despite the acceptance of dietary restrictions and these drugs, they do

not treat the underlying cause of the disease. We believe that AEB1102 represents a potential therapeutic candidate to treat the excess levels of arginine resulting from Arginase I deficiency.

#### Emerging areas in cancer therapy

Cancer is the second-leading cause of death in the United States. The National Cancer Institute estimates that in 2016 there were approximately 1.7 million new cases and approximately 596,000 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.

Beyond chemotherapeutics and targeted drug therapies, several new approaches to the development of novel cancer treatments are underway. These approaches include, but are not limited to treatment with drugs or other methods that stimulate the immune system to attack cancer cells, antibody drug conjugates that carry a powerful chemotherapy payload that is only released into targeted cancer cells, drugs that target the changes in gene activity that occur in cancer cells and drugs that target oncogenic drivers in patients with tumor types that harbor genetically similar alterations.

We believe that the altered metabolism of cancer cells—the atypical uptake and break down of nutrients—also provides an opportunity to develop important new cancer treatments. Cancer cells rapidly change how they take-up and utilize nutrients. These adaptations fuel tumor growth and protect cancer cells from the damage caused by reactive oxygen species, or ROS, and various immune system responses. However, while cancer cell metabolic abnormalities fuel tumor growth, 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 single agent and in combination with existing or emerging standards of care. Additionally, even though the dependence of different cancers on specific amino acids has been known for many years, it has not been widely exploited in the clinical setting.

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 an *E. coli*-derived enzyme, Oncaspar (pegaspargase) in combination with chemotherapy generates much improved remission rates as compared to chemotherapy alone. In addition, arginine dependence of tumors has been reported in the scientific and medical literature to result in responses to a microbial-derived arginine-degrading enzyme in trials with AML, mesothelioma, and melanoma. However, despite the reported clinical impact, this microbial-derived arginine degrading enzyme elicited an immune response that neutralizes the activity of the drug and therefore may result in limited clinical utility.

The use of microbial enzymes as therapeutics is often limited by an immune response to a foreign protein. We expect our enzyme product candidates, which are engineered from human proteins, will be less likely to elicit an immune response as compared to microbial enzymes, and to date we have not observed any patients in our clinical trials who have experienced an immune response to, or an adverse event that suggested an immune response to, AEB1102. We believe our technology should provide greater flexibility with respect to the target amino acids that can be addressed.

By depriving cancer cells of what we believe are key amino acids via our engineered human enzyme product candidates, we provide a novel approach that, when used alone or in combination with existing or emerging standards of care, has the potential to be a new and effective treatment paradigm for cancer patients. Published literature suggests that a variety of cancers could potentially respond to amino acid deprivation resulting from enzyme therapies, which offers us many potential targets for cancer treatment opportunities.

#### Our Development Programs

The following table summarizes our development programs:

##### AEB1102 (pegzilarginase)

AEB1102 is human Arginase I, engineered to reduce arginine levels to treat patients with Arginase I deficiency, and arginine-dependent solid tumors and the hematological malignancies AML and MDS. Following completion of dosing for the first two adult patients in our Phase 1 clinical trial for the treatment of patients with Arginase I deficiency, we submitted a protocol amendment in November 2016 to broaden the scope of our Phase 1 trial into a Phase 1/2 trial. The amended



protocol includes dosing of pediatric patients (two and older) and weekly repeat dosing, with the intent to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical response of AEB1102 in patients with this IEM. In the first quarter of 2017, we received IRB approval for the Phase 1/2 protocol for the treatment of patients with Arginase I deficiency at two clinical trial sites. In March 2017, we received an information request from the FDA which included comments and recommendations on the protocol amendment and a request for supporting documents based on their review of our completed toxicology studies, our dose escalation plan and our information to support the inclusion of pediatric patients. As recommended by the FDA, we replied with supporting information and requested a follow-up meeting. At this time, we believe our Phase 1/2 protocol provides an appropriate path to evaluate the safety and tolerability of AEB1102 in pediatric patients, and pending FDA feedback, we plan to initiate dosing in pediatric patients in the middle of 2017. In March 2017, we announced results from the first two adult patients in our Phase 1 clinical trial for the treatment of Arginase I deficiency at the ACMG Annual Meeting. We intend to continue enrollment of adult patients and plan to dose additional adult patients in the middle of 2017. Topline data from this trial is expected in the first half of 2018.

We are currently conducting two Phase 1 clinical trials. In October 2015, we initiated our Phase 1 dose escalation trial in patients with advanced solid tumors. We expect to announce results of this Phase 1 dose escalation in patients with advanced solid tumors and anticipate initiating expansion arms in specific solid tumor types, potentially in combination with existing or emerging standards of care, in the fourth quarter of 2017 or the first quarter of 2018. We are also conducting a Phase 1 dose escalation trial in patients with the hematological malignancies AML and MDS and expect to announce results for this trial in the fourth quarter of 2017 or the first quarter of 2018. After the completion of these dose escalation trials, we plan to initiate expansion arms in both specific solid tumors and AML and MDS. If we see compelling evidence of anti-tumor activity in the expansion phase, we plan to meet with regulatory authorities to discuss expedited regulatory strategies. Additionally, we plan to initiate a Phase 1b/2 trial, potentially in combination with existing or emerging standards of care in one or more solid tumor types and hematological malignancies.

#### AEB1102 background, preliminary clinical data in oncology

AEB1102 is being evaluated in two ongoing Phase 1 clinical trials in oncology indications. The Phase 1 clinical trial in patients with advanced solid tumors is an ongoing, open-label, multiple dose, dose-escalation trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of AEB1102. The primary objectives of the dose escalation stage are to determine the maximum tolerated dose, as well as to determine the safety, tolerability, and pharmacokinetic profile of AEB1102. The inclusion criteria include patients with locally advanced or metastatic solid tumors. These include adult patients whose tumors have failed to or progressed under standard treatment, cannot tolerate standard therapies or for which no standard therapy exists. We expect that up to 48 patients will be enrolled in the dose-escalation portion of the trial, depending on the number of dose levels studied and the adverse effects observed.

This Phase 1 trial was initiated in October 2015. To date, we have treated 8 cohorts consisting of 29 patients in total.

The following charts show a persistence of active AEB1102 in the blood over time and a dose-dependent reduction in blood arginine in patients with advanced solid tumors:

The data presented are preliminary and are subject to change. While these data provide proof-of-mechanism for AEB1102 in humans, these data may not necessarily be predictive of the final results of all patients intended to be enrolled in this Phase 1 trial or in future trials. While we have seen serious adverse events in this trial, including hypercalcemia, bacteremia, pericardial effusion, respiratory failure and death due to progressive cancer, to date these events were considered to be related to the underlying cancer and not considered to be related to AEB1102. The safety profile observed in the study supports continued dose escalation.

AEB1102 is being evaluated in a second Phase 1 trial for the treatment of the hematological malignancies AML and MDS. This Phase 1, multicenter, single-arm, open-label, dose escalation trial of AEB1102 for the treatment of hematological malignancies is designed to assess the safety and tolerability of AEB1102 as a single agent. The trial is enrolling patients with relapsed or refractory AML or MDS refractory to hypomethylating agents. Key objectives of the trial include determining the maximum tolerated dose, pharmacokinetics, pharmacodynamics (including reduction of circulating levels of arginine) and the recommended Phase 2 dose. An expansion cohort will be enrolled at the maximally tolerated or biologically relevant dose. We expect that up to 48 patients will be enrolled in the dose escalation portion of this trial and an additional ten patients will be enrolled at the maximum tolerated dose level to further evaluate safety at this dose level.

To date, three cohorts consisting of a total of 11 patients have been treated and a reduction in blood arginine levels has been observed in all patients. Given the nature of the patient population enrolled in this trial, we expect to and have observed serious adverse events in some of these patients. These serious adverse events have included a rise in white blood cell counts, fever, gout, pain, low potassium, pneumonia, worsening of the patients' underlying cancer progression, and death due to cancer progression. To date, only one serious adverse event, consisting of nausea and vomiting, has been considered to be possibly related to AEB1102.

At the end of our Phase 1 dose escalation in solid tumors, we intend to initiate expansion arms in different tumor types, which we have yet to determine. We anticipate that up to 75 patients may be enrolled in these expansion arms. The primary objective of the expansion phase is to assess safety and preliminary antitumor efficacy across these tumor types. These tumor types will be selected based on the biology underlying their development and the preclinical evidence generated by our research team. We also intend to initiate an additional Phase 1b/2 expansion trial to evaluate AEB1102, potentially in combination with an existing or emerging standard of care in one or more solid tumor types and hematological malignancies.

The selection of the solid tumor types for the Phase 1 expansion arms arises from our biomarker strategy, which is composed of two parts. First, we plan to confirm and extend the published scientific literature on the biomarkers of arginine dependence in multiple tumor types. Based on those data, we plan to further assess the predictive value of the biomarkers in patient-derived xenograft models, which are based on testing drug activity in patient tumor fragments. The results of these experiments, along with the results from our dose-escalation stage, will inform the choice of specific cancer indications for our expansion arms. If we use a biomarker-based test to identify and only enroll patients in clinical trials with tumors that express the biomarker, we expect that the FDA will require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate for that indication.

#### Arginase I deficiency background

Arginase I deficiency is a rare genetic disorder caused by mutations in the Arginase I gene, ARG1, leading to the inability to degrade arginine in the urea cycle. Patients with this disease are predisposed to neurologic symptoms including cognitive deficits and seizures and frequently suffer from spasticity, loss of ambulation, and severe intellectual disability.

Arginase I deficiency is a urea cycle disorder, with a reported incidence of 1:350,000 to 1:1,000,000 live births. It is believed that approximately 500-600 individuals in the United States and Europe suffer from Arginase I deficiency.

Although Arginase I deficiency is a rare genetic disease, we believe our working relationships with the IEM health care providers, Urea Cycle Disorders Consortium, and the National Urea Cycle Disorders Foundation patient advocacy group will assist in the identification of candidates for our clinical trials. Through these relationships, we have identified more than 40 treating physicians with over 50 patients with Arginase I deficiency in the United States and Europe to date. Because neonatal blood testing for this disorder did not become common in the United States until 2006, we believe that approximately half of those individuals identified in the United States are younger than 18. However, due to screening requirements and enrollment restrictions in our amended clinical trial protocol, or any additional restrictions that may be imposed by the FDA, not all pediatric patients, if any at all, may be eligible for inclusion in our Phase 1/2 trial in the United States. The onset of symptoms typically occurs between one and three years of age and diagnosis in the United States most often occurs through newborn blood screening for this disease, which takes place in 32 U.S. states. Because the symptoms of Arginase I deficiency are similar to a number of other ailments, including cerebral palsy, we believe the



incidence and prevalence of Arginase I deficiency are likely underestimated in regions such as Europe that do not mandate newborn blood screening for this disease.

There is no approved therapeutic agent that addresses the cause of Arginase I deficiency, although the medical literature suggests that disease progression can be slowed with strict adherence to dietary protein restriction. Dietary modification, which requires the use of specially formulated supplements, can reduce plasma arginine levels. This therapy is inadequate for treating the majority of patients with Arginase I deficiency, is difficult to manage, is poorly tolerated and is expensive. Therapy with the ammonia scavenging drugs RAVICTI (glycerol phenylbutyrate) or BUPHENYL (sodium phenylacetate) can be used to reduce elevated ammonia levels but does not appear to affect circulating arginine. Liver transplantation has been reported to be effective in patients to achieve normalization of arginine levels, but despite these successes, this intervention is available to only a small fraction of patients and carries a significant risk of mortality and morbidity.

The lack of existing treatment options that directly address the cause of Arginase I deficiency points to the need for a therapy that will lower arginine levels to within the normal range and promote the lifelong maintenance of normal arginine levels. The development of such a therapeutic and its initiation early in a patient's life could potentially minimize the exposure to the neurotoxic effects of arginine and its metabolites, and offer the potential for normal development in these patients.

#### AEB1102 clinical development in Arginase I deficiency

AEB1102 is intended to replace the function of Arginase I in patients, and return their elevated arginine levels to the normal physiological range. Normalization of arginine levels is anticipated to slow or halt the progression of the disease in these patients. Our Phase 1/2 clinical trial for the treatment of patients with Arginase I deficiency will assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical response of AEB1102 in patients with this IEM.

Topline results of our Phase 1 clinical trial have shown AEB1102 to be effective in lowering blood arginine in two adult patients with Arginase I deficiency. AEB1102 was well tolerated with no adverse events or other clinical changes reported in this trial. Plasma arginine levels decreased in a dose-proportional manner after AEB1102 infusions. One patient stopped dose escalation after plasma arginine levels measured below 40  $\mu$ M after the second dose (0.03 mg/kg), and the other patient stopped after the third dose (0.06 mg/kg) after plasma arginine levels measured below 40  $\mu$ M.

The following chart shows the pharmacodynamic effect of AEB1102 administration in our Phase 1 clinical trial in two adult patients with Arginase I deficiency.

We have obtained orphan drug designation from the FDA and EMA, and Fast Track Designation from the FDA, for AEB1102 for the treatment of patients with Arginase I deficiency. The FDA may grant orphan drug designation for drugs



or biologics designed to treat disorders affecting fewer than 200,000 people in the United States. If the data from our Phase 1/2 trial is supportive, we may seek to accelerate our development plan for AEB1102 by requesting to use established regulatory pathways, such as Breakthrough Therapy Designation. Regardless of whether we receive this designation, we anticipate initiating a Phase 3 registration directed trial enrolling 15 to 30 patients. If successful, we expect that this trial would support a BLA filing with the FDA.

We have met with the FDA on two occasions regarding the pathway for potential approval of AEB1102 for the treatment of Arginase I deficiency. Although the FDA recommended in our 2014 Pre-IND meeting that we measure age appropriate neurocognitive outcomes in our trials for marketing approval under the regular approval pathway, the FDA has agreed that the primary endpoint of our Phase 2 and Phase 3 trials could be the normalization of blood arginine levels; provided that we can provide adequate justification that normalization of plasma arginine in the target population is reasonably likely to predict clinical benefit. To do this, we believe the FDA expects some evidence of consistent trends in the stabilization or improvement of clinical signs and symptoms of Arginase I deficiency to be observed in the Phase 3 trial to support the primary endpoint. The FDA has suggested that we investigate multiple endpoints that can show a clinically meaningful benefit, such as neurocognitive outcomes and quality-of-life measurements, and not necessarily focus on achieving a statistically significant result (usually measured by a statistical value that indicates the likelihood that the result is not due to chance) on a single clinical endpoint, given the small number of patients expected to be enrolled in this trial. The FDA stated that the Phase 3 trial length and design will need to be adequate to assess safety in the target population, stated that it is not clear that the time needed to show an effect on a biomarker will be an adequate duration to characterize safety and recommended that we reach agreement with the FDA on the duration of such a trial if we decide to pursue an accelerated approval development plan. Finally, if we obtain expedited approval, we may be required to conduct a post-approval controlled trial that verifies clinical benefit in neurocognitive outcomes, and the FDA has stated that it expects the verification study to be underway at the time of accelerated approval. In March 2017, we received an information request from the FDA which included comments and recommendations on the protocol amendment and a request for supporting documents based on their review of our completed toxicology studies, our dose escalation plan and our information to support the inclusion of pediatric patients. As recommended by the FDA, we replied with supporting information and requested a follow-up meeting. At this time, we believe our Phase 1/2 protocol provides an appropriate path to evaluate the safety and tolerability of AEB1102 in pediatric patients, and pending FDA feedback, we plan to initiate dosing in pediatric patients in the middle of 2017. With respect to Arginase I deficiency, we do not expect to need FDA regulatory approval of any diagnostic test prior to obtaining approval, if any, of AEB1102 for that indication. A widely adopted neonatal blood test for Arginase I deficiency currently exists, which is a part of mandatory newborn screening in 32 U.S. states and is incorporated into routine care for diagnosis and treatment of patients with Arginase I deficiency.

#### AEB1102 background in oncology

We are targeting the dependence of some cancers on the amino acid arginine using AEB1102. Arginine is considered a semi-essential amino acid since in some circumstances cells cannot make sufficient amounts of arginine. These circumstances include conditions of enhanced proliferation, tissue injury or stress. 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 and metastasis in experimental tumor models.

Many types of cancers lose the ability to synthesize intracellular arginine, principally due to deficiency in the expression of any one or more of the following enzymes—ornithine transcarbamoylase, or OTC, argininosuccinate synthase1, or ASS1 and argininosuccinate lyase, or ASL. As a result, these cancers depend on extracellular arginine uptake. When deprived of this tumor-essential nutrient, cancer cells die, establishing a correlation between their inability to synthesize arginine and vulnerability to arginine deprivation. As set forth in the figure below, based on data from our preclinical studies and the published scientific and medical literature, Arginase I degrades arginine to

ornithine and urea. Ornithine cannot be used to make arginine by any cancer cells that lack expression of OTC, ASS or ASL.

a Rabinovich et al (2015) "Diversion of aspartate in ASS1-deficient tumors fosters de novo pyrimidine synthesis"  
Nature

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 a predictive biomarker for arginine dependent cancer cells. Our preclinical research has focused on the reduced or loss of expression of ASS1 as the predominate cause of tumor arginine dependence.

b BioPortal: Gao et al. (2013) "Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal" Sci. Signal. and Cerami et al. (2012) "The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data" Cancer Discovery.

Low or no expression of ASS1 in patient derived xenograft models from patients with melanoma or small lung cancer results in sensitivity to arginine depletion by AEB1102 in preclinical models, as shown below.

Emerging cancer therapies such as immune checkpoint inhibitors have demonstrated a significant clinical benefit in melanoma. When AEB1102 was tested in combination with immune checkpoint inhibitors targeting PD-1, PD-L1, or CTLA-4 additive or synergistic inhibition of tumor growth was observed in CT-26, MC-38, and Lewis Lung mouse tumor allograft models. One example of a synergistic response in combination with a PDL-1 inhibitor in our preclinical studies is shown below.

In this preclinical study, when AEB1102 was administered in combination with anti-PD-L1 for at least 8 weeks, a 37% frequency of complete tumor regression was observed. When the tumor-free mice were re-injected with fresh tumor cells, the tumor failed to establish, suggesting the development of an immune memory response as a result of the previously administered combination therapy of AEB1102 and anti-PD-L1 monoclonal antibody.

#### Targeting cysteine/cystine and oxidative stress for oncology

Reactive oxygen species, or ROS, have been widely reported in the scientific and clinical research literature to have enhanced production in tumors creating oxidative stress, resulting in damage to lipids, membranes, structural and functional proteins and DNA of the tumor cells. Major sources of oxidative stress in cancer include: metabolic activities due to aberrant growth-promoting pathways, infiltrating inflammatory cells, as well as standards of care such as chemotherapy and radiation therapy. The antioxidant glutathione is a key natural protector of ROS-mediated damage and has an enhanced role in protecting tumor cells from high levels of ROS. To survive in this hostile environment, cancer cells produce high levels of glutathione which preferentially reacts with and neutralizes the otherwise damaging ROS. Glutathione cannot be transported into cells from outside the cell, and must be synthesized in each cell. In order to satisfy the tumor's demand for glutathione, an adequate supply of cysteine/cystine is required. Reducing available

cysteine/cystine from outside the cell decreases the levels of glutathione, increasing ROS-related damage to cancer cells and triggering cancer cell death.

The production of ROS is both an initiator as well as a promoter of cancer, requiring increased production of glutathione for the cancer cells to survive. However, many cancer treatments are also cytotoxic through the production of ROS. This apparent paradox is receiving increased attention as a potential tumor vulnerability, and underlies the mechanistic rationale for selective tumor killing by using a therapeutic enzyme to reduce available cysteine/cystine in the blood. While chemotherapy and radiation therapies are often highly efficient at eliminating the bulk of cancer cells, treatment-resistant cancer stem cells are highly resistant to ROS-mediated damage and survive anti-cancer therapy. These cancer stem cells are thought to be a cause of patient relapse.

Cancer stem cells are protected from ROS stress through increased glutathione production in both hematological malignancies and solid tumors. Based on an extensive body of evidence from the scientific and clinical research literature, we believe targeting the glutathione dependence of cancer will not only have direct anti-tumor activity but may also show synergy in combination with standards of care, depleting the cancer stem cell populations to provide a prolonged benefit to patients.

### AEB3103

AEB3103, our lead product candidate in this program, is an engineered human enzyme that targets the degradation of the amino acid cysteine/cystine. To our knowledge, the human genome does not encode a native cysteine- or cysteine-degrading enzyme. Initial efficacy testing in preclinical models demonstrated significant depletion of glutathione and significantly increased levels of ROS in HMVP2 prostate cancer cells. As shown below, in vivo AEB3103 demonstrated a statistically significant depletion of glutathione and significantly increased levels of ROS in HMVP2 prostate cancer cells. The treatment appeared to be well tolerated as the tested animals showed no change in appetite or weight loss.

As shown in the following chart, AEB3103 also improved survival in a mouse genetic model of chronic lymphocytic leukemia.

### Targeting methionine dependence for oncology

The dependence of tumors on the essential amino acid methionine for survival has been described extensively in the scientific and medical literature, with the demand of some tumors for methionine far exceeding that of normal tissues. This dependence has been exploited in the clinic as a diagnostic where an analog of methionine is the preferred contrast agent for imaging of glioblastomas, astrocytomas and melanoma metastases to the brain. This is because methionine supports five metabolic pathways which promote tumor growth, protecting tumor cells from a hostile environment, and ultimately forms the rationale for using methionine starvation to target tumor cells. Over 40 years of research on tumor methionine dependence has been built on the use of a bacterial methionine-degrading enzyme. This microbial enzyme never advanced in clinical development, but provided a strong rationale for targeting methionine dependence in tumors.

The finding of tumor methionine dependence led to efforts to attempt dietary manipulation as an anti-cancer therapy. These efforts provided evidence of limited activity, but did not reduce methionine levels sufficiently. Enzyme-mediated methionine depletion in animals has resulted in far lower serum levels than nutritional restrictions can achieve, suggesting that our therapeutic approach with an engineered human methionine-degrading enzyme may achieve meaningfully improved efficacy in combination with standard of care.

Because there are specific metabolic pathways dependent on methionine metabolism, we believe methionine depletion used in combination with a variety of chemotherapeutics will be complementary to enzyme-mediated methionine depletion in blood, and may result in synergistic effects. We anticipate new treatment paradigms utilizing this approach, if successfully developed and approved, will have a significant impact with both improved patient responses and long term outcomes.

### AEB2109

AEB2109, our lead enzyme in this program, is an engineered human enzyme that targets the degradation of the amino acid methionine. To our knowledge, the human genome does not encode a native methionine-degrading enzyme. 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 that has been recognized for over 40 years, but 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.

### AEB4104 and additional pipeline opportunities

Our ongoing research efforts have identified various opportunities to leverage our expertise in the field of enzyme biochemistry to develop product candidates targeting various IEM and tumor metabolism mechanisms. We are currently in the early discovery stages for an engineered human enzyme therapy with AEB4104, the most advanced enzyme in that program, targeting the reduction of elevated levels of the amino acid homocysteine. Elevated blood levels of this amino acid arise in the IEM called classical homocystinuria. We believe that classical homocystinuria represents a viable market opportunity and significant unmet medical need, which we plan to address by continuing our development of AEB4104 and related enzymes. Regarding oncology indications, we will continue to explore other amino acids for targeted enzyme treatments in combination with emerging and current standards of care such as chemotherapy and radiation therapy. We



plan to concurrently develop multiple product candidates targeting diseases with clear mechanisms of action and balancing research and development in rare genetic diseases and oncology to maximize value.

## 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, 2016, we are the owner of five U.S. patents, expiring between 2029 and 2031, absent any extensions, three of which are directed to the compositions methods of preparing, and methods of using AEB1102 (pegzilarginase), and two of which are directed to compositions of AEB4104. As of December 31, 2016, we also owned two pending U.S. utility patent applications, one of which is related to pharmaceutical compositions of AEB1102, and the other directed to methods for identifying and selecting primate cystathionine gamma-lyase variants having L-methionine degrading activity.

As of December 31, 2016, we also controlled two U.S. utility patent applications, exclusively licensed to us by the Board of Regents of The University of Texas System, or the University, including one related to compositions of AEB2109 and one related to compositions of AEB3103 and their use in cancer treatment. Any patents issuing from the foregoing owned or licensed U.S. patent applications are expected to expire in 2034, absent any adjustments or extensions.

As of December 31, 2016, we owned a total of five patents and five applications in foreign jurisdictions variously including: Australia, Canada, China, Europe, Japan, Hong Kong and South Korea. Any issued patents, or those issuing from these foreign patent applications, are expected to expire between 2029 and 2031, absent any adjustments or extensions. These foreign patent applications and patents comprise claims that relate to the compositions of AEB1102 and AEB4104 and methods of use of AEB1102 for the treatment of cancer. As of December 31, 2016, we also controlled 14 pending international patent applications in Australia, Canada, China, the European Patent Office, Israel, Japan and Korea, which are also exclusively licensed to us by the University, with claims directed to compositions and methods of use of AEB2109 and compositions and methods of use of AEB3103. Any patents issuing from these applications are expected to expire in 2034, 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, AECase, Inc., or AECase, and AEMase, Inc., or AEMase, entered into license agreements with the University under which the University has granted to AECase and AEMase exclusive, worldwide, sublicenseable licenses. The University granted to AECase a license under a patent application relating to the right to use 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. 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.

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 \$500,000 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, 2016, we have paid \$41,000 under these license agreements.

#### Sponsored Research Agreement

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 on September 24, 2014, January 15, 2015, August 10, 2015, November 5, 2015, January 7, 2016, and August 3, 2016. 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 will expire on August 31, 2017, and we have the option of extending the research program under mutually agreeable support terms. We can terminate the SRA with 60 days' notice to the University. The University can terminate the SRA for our material breach that remains uncured 60 days after notice from the University. With respect to intellectual property that results from the sponsored research, each party owns any such intellectual property that it solely creates and we jointly own with the University any such intellectual property that we jointly create. We have an option to negotiate a license to the University's interest in any such intellectual property and any such license agreement is expected to be on terms substantially similar to the existing license agreements described above. If we fail to enter into such a license agreement within six months of the date we exercise our option (or such longer period of time as we may mutually agree), the University would be free to grant licenses under the applicable intellectual property to third parties. The maximum permitted cost of the sponsored research to us is approximately \$2.2 million. This increases if we agree to extend the research program beyond August 31, 2017. As of December 31, 2016, we have paid \$1.8 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. As of December 31, 2016, we have recognized \$10.7 million in revenue under the Grant Contract and collected \$9.6 million in grant proceeds. The Grant Contract expires on May 31, 2018.

Pursuant to the Grant Contract, we grant 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 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 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. 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 IEM and cancer metabolism.

**Inborn errors of metabolism.** With respect to AEB1102 for Arginase I 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 I deficiency. The current method for treating patients with Arginase I deficiency includes dietary restriction, which appears to slow the disease progression, as well as treatments such as Hyperion Therapeutics' RAVICTI (glycerol phenylbutyrate) and BUPHENYL (sodium phenylacetate) which lower blood-ammonia levels.

**Cancer metabolism.** 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. While our product candidates may compete with many existing drug and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product candidates will not be competitive with them. 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, these therapies all 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 Biocancer Treatment International's pegylated native human Arginase I. Additionally, Calithera Biosciences is targeting a therapy that inhibits Arginase I 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 AEB1102.

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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 studies and intend to do so for our future clinical studies as well. We intend to identify and qualify additional manufacturers to provide potential alternative sources for the active pharmaceutical ingredient and fill-and-finish services for AEB1102 as the compound progresses through clinical development, prior to seeking marketing approval from FDA. We believe we have sufficient supplies of AEB1102 for our ongoing and planned Phase 1 clinical trials.

#### The KBI Agreement

In December 2013, we entered into a Master Services Agreement, or KBI Agreement, with KBI Biopharma, Inc., or KBI, in which KBI agreed to research, develop and manufacture the active pharmaceutical ingredient for AEB1102 in exchange for cash and shares of our Series A convertible preferred stock. In June 2015, we amended the KBI Agreement to also permit us to exchange Series B convertible preferred stock for such research, development and manufacturing services. The KBI Agreement was further amended in June 2015 to convert the remaining unmet milestone awards from share-based payments to cash. The KBI Agreement has an initial three-year term and automatically renews for successive additional one-year terms until the services are completed. The KBI Agreement may be terminated by either party for a breach that is not remedied within thirty days after notice or in the event of a bankruptcy by either party. We may terminate the KBI Agreement upon sixty-days written notice. For termination other than a material breach by KBI, we must pay for all services conducted prior to the termination and to wind down the activities.

#### The LSNE Agreement

In November 2014, we entered into a Master Services Agreement, or LSNE Agreement, with Lyophilization Services of New England, Inc., or LSNE, in which LSNE agreed to manufacture the finished product of AEB1102 for clinical testing in exchange for cash. The LSNE Agreement has a one-year term that we may unilaterally extend for successive one-year periods upon written notice. The LSNE Agreement may be terminated for either party for a material breach that is not remedied within thirty-days after notice or in the event of a bankruptcy by either party. We may terminate the contract for convenience upon written notice, but must pay termination fees.

We do not own or operate manufacturing facilities for the production of clinical quantities of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. The use of contracted manufacturing is relatively cost-efficient and has eliminated the need for our direct investment in manufacturing facilities and additional staff early in development.

For our biomarker and companion diagnostic strategies, we will rely on third-party vendors for the development and execution of our tests. If we choose to develop a biomarker-based test, including a companion diagnostic, for any of our therapeutic enzymes, we may rely on one or more third parties to manufacture and sell a single test.



## 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 the 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.

Pursuant to the 21st Century Cures Act, which was enacted on December 13, 2016, the manufacturer of an investigational drug 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. This requirement applies on the later of 60 calendar days after the date of enactment of the law or the initiation of a Phase 2 or Phase 3 trial of the 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 annual product and establishment user fees. While these fees are typically increased annually, they decreased from Fiscal Year 2016 to Fiscal Year 2017. 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 indication studied.

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.

#### 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, 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 United States Patent and Trademark Office 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. To date, only a handful of biosimilar products 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 Biologics Evaluation and Research and by the FDA's Center for Devices and Radiological Health.

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 an application fee, which exceeds \$230,000 for most PMAs. In addition, PMAs for certain devices 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 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 establish registration and device listings 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.

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

In March 2010, President Obama enacted the ACA, which 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 new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals beginning in 2014 and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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. In addition, it is possible that there will be further legislation or regulation that could harm our business, financial condition and results of operations.

#### 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

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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, 2016, we had a total of 30 full-time employees, all located in the United States. 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, 2016, 2015 and 2014 and our total assets as of December 31, 2016 and 2015, 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. You may also read and copy, at SEC prescribed rates,

any document we file with the SEC at the SEC's Public Reference Room located at 100 F Street, N.E., Washington D.C. 20549. You can call the SEC at 1-800-SEC-0330 to obtain information on the operation of the Public Reference Room.

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## 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 an early-stage biotechnology company. We began operations as a limited liability company in December 2013 and converted to a Delaware corporation in March 2015. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our technology, identifying potential product candidates, undertaking nonclinical studies, and preparing for, commencing and conducting initial clinical trials of our most advanced product candidate, AEB1102.

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 recently begun clinical development of AEB1102. Our ability to generate revenue and become profitable depends upon our ability to successfully complete the development of any of our product candidates, including AEB1102, for any of our target indications and to obtain necessary regulatory approvals. To date, we have recognized revenue solely from a 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, 2016, 2015, and 2014, we reported a net loss of \$21.7 million, \$11.3 million, and \$10.3 million, respectively. As of December 31, 2016, we had an accumulated deficit of \$45.3 million. We have financed our operations primarily through private placements of our preferred stock, the initial public offering, or IPO, of our common stock, which

closed on April 12, 2016, and collection of a research grant. We have devoted substantially all of our efforts to research and development. We have only recently initiated clinical development for AEB1102 for the treatment of advanced solid tumors, Arginase I deficiency and the hematological malignancies AML and MDS. 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;

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- 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;
- ultimately 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 to modify protocols of our clinical trials or perform studies in addition to those that we currently anticipate. Even if AEB1102, 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 in the nonclinical development stages for most of our product candidates, and have only recently initiated clinical development for AEB1102 for the treatment of advanced solid tumors, Arginase I deficiency and the hematological malignancies AML and MDS. 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 AEB1102.

In order to execute on our strategy of advancing the clinical development of our product candidates, we are conducting three clinical trials for AEB1102, consisting of one Phase 1/2 clinical trial for the treatment of Arginase I deficiency and two Phase 1 clinical trials for the treatment of patients with advanced solid tumors and the hematological malignancies AML and MDS. We have designed the planned expansion portion of our Phase 1 trial of AEB1102 for the treatment of advanced solid tumors, predicted to be dependent on arginine, based on our biomarker studies in archival tumor samples and in patient-derived xenograft efficacy studies, or studies involving the growth of tissue or cells from one species in a different species. If our product candidate fails to work as we expect, our ability to assess the therapeutic effect, seek regulatory approval or otherwise begin or further clinical development, could be compromised. This 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 AEB1102, in clinical trials specific for a given tumor type and this may 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 AEB1102, 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 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.

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 or on acceptable terms, we would be forced to delay, reduce or eliminate our discovery and nonclinical development programs or any future clinical development or commercialization efforts.

Based upon our planned use of the net proceeds from our IPO, we estimate such funds will be sufficient for us to fund our Phase 1/2 clinical trial for the treatment of patients with Arginase I deficiency and our two ongoing Phase 1 clinical trials for the treatment of patients with advanced solid tumors and the hematological malignancies AML and MDS. 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. To the extent that we raise additional capital through the sale of equity or convertible debt securities, 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, AEB1102. All of our product candidates, other than AEB1102, are still in nonclinical development or nonclinical testing, and for AEB1102, the early stages of clinical development. Existing and future clinical trials of our product candidates, including AEB1102, 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, AEB1102, for the treatment of patients with Arginase I deficiency and patients with advanced solid tumors and the hematological malignancies AML and MDS. 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 AEB1102. The success of AEB1102 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;
- 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 only recently initiated clinical trials of our lead product candidate AEB1102, and 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 and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process, and we only recently commenced clinical trials for AEB1102 for the treatment of patients with advanced solid tumors, Arginase I deficiency and the hematological malignancies AML and MDS. Further, 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 for AEB1102 for the treatment of patients with Arginase I deficiency, advanced solid tumors, and the hematological malignancies AML and MDS, this data may not necessarily be predictive of the final results of all patients intended to be enrolled in these Phase 1 clinical trials or in future trials. Furthermore, our ongoing Phase 1 clinical trials for the treatment of advanced solid tumors and the hematological malignancies AML and MDS, will evaluate the safety of our product candidates, and we will not be evaluating the efficacy of our product candidates in these early trials. 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 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 FDA, EMA, MHRA or any similar foreign regulatory agency 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 FDA, EMA, MHRA or a comparable foreign regulatory authority 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;
- 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;
- 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;
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a clinical hold for any of our ongoing or planned clinical trials, including for AEB1102, 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;

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- 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 I deficiency or patients with tumors or hematological malignancies, including the identification of patients with Arginase I 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 or hematological malignancies dependent on arginine that AEB1102 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;
- 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;
- 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, we withdrew our initial IND for the treatment of Arginase I deficiency in July 2015 in order to comply with new draft guidance issued by the FDA that required additional toxicology studies. In addition, we originally proposed including subjects younger than age 18 in our initial Phase 1 trial in patients with Arginase I deficiency; however, the FDA stated that enrollment in this Phase 1 trial must currently be limited to adult patients 18 years and older. In November 2016, we submitted a protocol amendment to broaden the scope of our Phase 1 clinical trial for the treatment of Arginase I deficiency into a Phase 1/2 trial. The amended protocol includes dosing of pediatric patients (two and older) and weekly repeat dosing. In March 2017, we received an information request from the FDA which included comments and recommendations on the protocol amendment and a request for supporting documents based on their review of our completed toxicology studies, our dose escalation plan and our information to support the inclusion of pediatric patients. While we have replied with supporting information and believe that our Phase 1/2 protocol provides an appropriate path to evaluate the safety and tolerability of AEB1102 in pediatric patients, the FDA may disagree with us, require additional information or studies to be conducted, or impose conditions that could delay or restrict our planned clinical activities. 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 FDA, EMA, MHRA or comparable foreign regulatory 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 AEB1102 for the treatment of patients with advanced solid tumors, Arginase I deficiency and the hematological malignancies AML and MDS. 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 number of patients the FDA, EMA, MHRA or another applicable regulatory authority 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 recently initiated our Phase 1 clinical trials for AEB1102 for the treatment of patients with advanced solid tumors, Arginase I deficiency and the hematological malignancies AML and MDS. 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 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 have only recently initiated our clinical trials for AEB1102 for the treatment of patients with advanced solid tumors, Arginase I deficiency and the hematological malignancies AML and MDS. Given the nature of the patient population enrolled in these trials, we have observed and expect to continue to observe serious adverse events which could be related or unrelated to AEB1102. For example, in each of our Phase 1 trials for AEB1102 for the treatment of patients with advanced solid tumors and the hematological malignancies AML and MDS, we have observed serious adverse events in some patients, including death. To date, only one serious adverse event, consisting of nausea and vomiting, has been considered to be possibly related to the administration of AEB1102. Subjects in our ongoing and planned clinical trials may suffer significant serious adverse events, including those that are drug-related, or other side effects not observed in our nonclinical studies, including, but not limited to, immune responses, organ toxicities such as liver, heart or kidney or other tolerability issues. We have not dosed any of our other product candidates in humans.

Testing in animals, such as our primate studies for AEB1102, may not uncover all side effects in humans or any observed side effects in animals may be more severe in humans. For example, it is possible that patients' immune

systems may recognize our engineered human enzymes as foreign and trigger an immune response. This risk is heightened in patients who lack the target enzyme, as is the case with patients with Arginase I deficiency that we are treating in our recently initiated Phase 1/2 trial and our future trials for this IEM. In addition, our product candidates such as AEB1102 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 AEB1102 are engineered from the human genome, AEB1102 is produced in *E. coli*. This manufacturing process could lead AEB1102 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 FDA, EMA, MHRA or comparable regulatory authorities outside the United States. More specifically, many of our product candidates, including AEB1102, initially target indications that may be characterized as orphan markets, which can prolong the clinical trial timeline for the regulatory process if sufficient patients cannot be enrolled in a timely manner. Arginase I deficiency, for example, is the least common of the urea cycle disorders, with a reported incidence of 1:350,000 to 1:1,000,000 live births. Urea cycle disorders are the IEM resulting from defects in the enzymes of the urea cycle, the process by which the human body detoxifies ammonia, a natural byproduct of protein metabolism. While there is currently a neonatal blood test to screen for Arginase I deficiency, it has only been in broad use in the United States since 2006 and is not commonly used in Europe. To date, the urea cycle disorder consortium and one national urea cycle disorder patient group have together identified approximately 40 treating physicians with over 50 patients with Arginase I deficiency in the United States and Europe. Because neonatal blood testing for this disorder did not become common in the United States until 2006, we believe that approximately half of those individuals identified in the United States are younger than 18. However, due to screening requirements and enrollment restrictions in our amended clinical trial protocol, or any additional restrictions that may be imposed by the FDA, not all pediatric patients, if any at all, may be eligible for inclusion in our Phase 1/2 trial in the United States.

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 I deficiency suffer from heightened levels of ammonia, or hyperammonemia. Hyperion Therapeutics, Inc., which has been acquired by Horizon Pharma plc, has gained approval for its product

RAVICTI (glycerol 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.

Even though we have obtained orphan drug designation for AEB1102 in the United States and Europe for the treatment of hyperargininemia, we may not obtain or maintain orphan drug exclusivity for AEB1102 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 that time period. The applicable period is seven years in the United States and ten years in Europe. 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.

On March 16, 2015, we obtained orphan drug designation in the United States for AEB1102 for the treatment of patients with hyperargininemia, also known as Arginase I deficiency. On July 14, 2016, we also received orphan drug designation in Europe for AEB1102 for the treatment of patients with Arginase I deficiency. A company that first obtains FDA or EMA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug 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 AEB1102 for the treatment of Arginase I deficiency, we may not be the first to obtain marketing approval for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical product candidates. 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.

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 I deficiency or who have advanced tumors or hematological malignancies 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 AEB1102, are based on

estimates. 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.

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 AEB1102 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 I deficiency include dietary protein restriction and, in some instances, ammonia-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. 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. 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 sometimes include patients suffering from Arginase I deficiency. Patients with Arginase I deficiency may also benefit from taking RAVICTI (glycerol phenylbutyrate). We also face intense competition from companies developing products and therapies to treat cancer. For example, Polaris Pharmaceuticals 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 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. 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. Congress and the new Trump administration have 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 I deficiency for AEB1102, 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 an early-stage clinical development company with a limited operating history, and, as of December 31, 2016, had only 30 employees, including five executive officers. We are highly dependent on the research and development, clinical and business development expertise of our executive officers, as well as the other principal members of our

management, scientific and clinical team. Any of our management team members may terminate their employment with us at any time. We do not maintain “key person” insurance for any of our executives or other employees.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, facilitate regulatory approval of and commercialize product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. For instance, we are currently in the process of searching for a new Chief Medical Officer. There is no assurance that a qualified individual will be found timely or engaged on acceptable terms. 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 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.

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

Despite the implementation of security measures, our internal computer systems and those of our strategic partners and third-parties on whom we rely are vulnerable to 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 the University of Texas at Austin and 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 and cause interruptions in our operations, the operations of our strategic partner the University of Texas at Austin, our other third-party strategic partners, or our manufacturers or suppliers, it could result in a material disruption of our product candidate development programs. For example, the loss of research data by University of Texas at Austin could delay development of our product candidates and 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.

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

We 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, discovery and clinical development capabilities. For example, we rely on the University of Texas at Austin to provide research under our sponsored research agreement, and we rely on a contract manufacturing organization, KBI BioPharma, Inc., or KBI, to manufacture and supply nonclinical and clinical trial quantities of the biological substance of our lead product candidate, AEB1102 and pipeline product candidates. We also expect to rely on KBI to manufacture and supply commercial quantities of AEB1102. Until we develop our own drug discovery capabilities, we will continue to depend on third parties such as the University of Texas at Austin for the identification of future targets for our product candidates.

We will rely on third-party CROs to conduct our ongoing and future planned clinical trials of AEB1102. 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, and we do not have any manufacturing personnel. 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, including KBI and Lyophilization Services of New England, Inc., 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, including KBI, 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, KBI is supplying, and is expected to continue to supply, the drug substance requirements for our ongoing and planned clinical trials with AEB1102. If KBI 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 KBI for certain studies related to potential commercial scale manufacturing of AEB1102 at a separate KBI facility, 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, including KBI, 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, including KBI, 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.

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.

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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 comply with FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, provide accurate information to the FDA or comparable non-U.S. regulatory authorities, comply with manufacturing standards we have established, 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, 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.

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 KBI's manufacturing 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 KBI's manufacturing 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 KBI's manufacturing 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 FDA, EMA, MHRA or other comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA, EMA, MHRA or other comparable foreign regulatory 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 FDA, EMA, MHRA or other comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks;
- the FDA, EMA, MHRA or other comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical programs or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the FDA, EMA, MHRA or other comparable foreign regulatory 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 FDA, EMA or other comparable foreign regulatory 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 AEB1102 for the treatment of hyperargininemia secondary to Arginase I 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 AEB1102 for the treatment of



hyperargininemia secondary to Arginase I 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 that have obtained fast track designation. 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.

Any product candidate for which we obtain marketing approval will be subject to extensive post-marketing regulatory requirements and could be subject to post-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 may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of any approved product. 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.

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 will be 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.

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.

More recently, in March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, 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 50% point-of-sale discounts off negotiated prices;

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- extension of manufacturers' Medicaid rebate liability to manage care initiation;
- 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, President Obama signed into law the American Taxpayer Relief Act of 2012, 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. More recently, President Trump has suggested that he plans to seek repeal of all or portions of the ACA, and he has indicated that he wants Congress to replace the ACA with new legislation. We cannot predict whether these challenges will continue or 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.

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 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 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 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 and China do not allow patents for methods of treating the human body. 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 the application may depend upon our ability to generate additional preclinical 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 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.

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. Under the Sponsored Research Agreement, we made payments of \$832,000, \$563,000, and \$386,000 for the years ended December 31, 2016, 2015, and 2014, respectively, to sponsor research in the laboratory of our director, Dr. George Georgiou, at the University of Texas at Austin on the engineering, optimization and initial animal validation of human enzymes to determine the systemic depletion of amino acids for cancer therapy and to analyze enzyme replacement for the treatment of patients having inborn metabolic defects.

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 AECase, Inc. and AEMase, Inc. each entered into an exclusive, worldwide license agreement, including the right to grant sublicenses, with the University of Texas at Austin for certain intellectual property owned by the University of Texas at Austin related to our product candidates AEB3103 and AEB2109. On January 31, 2017, we and the University of Texas at Austin entered into 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.

Our executive officers and directors, combined with our stockholders who each owned more than 5% of our outstanding common stock, including shares sold in our IPO, in the aggregate, beneficially own shares representing a majority of our capital stock as of December 31, 2016. 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.

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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.

We are not currently required to comply with the rules of the Securities and Exchange Commission that implement Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, and are therefore not required to make a formal assessment of the effectiveness of our internal control over financial reporting for that purpose until our annual report for the year ended December 31, 2017. Pursuant to Section 404, we will be required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles in the United States. We are not currently in compliance with, and we cannot be certain when we will be able to implement the requirements of Section 404(a). 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;

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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;

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• 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 IPO and may not use them effectively.

Our management has broad discretion in the application of the net proceeds from the IPO, 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 the IPO 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 IPO 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, 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. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline.

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 for up to five years. 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;

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- 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 will 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 will first be required to furnish a report by our management on our internal control over financial reporting for 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 February 2017, we entered into a separate lease agreement for approximately 3,250 square feet of laboratory space in Austin, Texas, which will expire in December 2017. We intend to add additional space if we add employees and expand geographically. We believe that our facilities are adequate to meet our needs for the immediate future, and that, should it be needed suitable additional space will be available on commercially reasonable terms to accommodate any such expansion of our operations.

#### ITEM 3. LEGAL PROCEEDINGS

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

#### ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.



## PART II

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

## Market Information and Holders

Our common stock is traded on the NASDAQ Global Market under the symbol "AGLE." Prior to April 6, 2016, there was no public market for our common stock. The table below summarizes the high and low sales prices of our common stock as reported on the Nasdaq Global Market.

|                              | High    | Low    |
|------------------------------|---------|--------|
| Year ended December 31, 2016 |         |        |
| Second Fiscal Quarter (1)    | \$11.99 | \$4.36 |
| Third Fiscal Quarter         | \$8.11  | \$3.96 |
| Fourth Fiscal Quarter        | \$6.99  | \$4.35 |

(1)The period reported for the second fiscal quarter is from April 6, 2016 through June 30, 2016.

As of March 16, 2017, there were 51 registered holders of record of our common stock, based on information provided by our transfer agent. The actual number of stockholders is greater than this number of registered record holders, and includes stockholders who are beneficial owners, but whose shares are held in "street name" by brokers and other nominees.

## 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, 2016. 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.

| \$100 investment in stock or index | Ticker | April 7, 2016 | December 31, 2016 |
|------------------------------------|--------|---------------|-------------------|
| Aeglea Biotherapeutics, Inc.       | AGLE   | \$ 100.00     | \$ 44.52          |
| NASDAQ Composite Index             | IXIC   | \$ 100.00     | \$ 111.03         |
| NASDAQ Biotechnology Index         | NBI    | \$ 100.00     | \$ 94.56          |

## 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. Pursuant to the IPO, we sold an aggregate of 5,481,940 shares of our common stock, including 481,940 shares of common stock sold pursuant to the underwriters' partial exercise of their option to purchase additional shares for aggregate gross proceeds of \$54.8 million. UBS Securities LLC, BMO Capital Markets Corp. and Wells Fargo Securities, LLC acted as joint-book-running managers of the offering and as representatives of the underwriters. Needham & Company, LLC acted as co-manager for the offering. The offering did not terminate before all of the securities registered in the registration statement were sold. On April 12, 2016, we closed the sale of such shares, resulting in net proceeds to us of \$47.3 million after deducting underwriting discounts and commissions of \$3.8 million and offering costs of \$3.7 million. No payments were made by us to directors, officers or persons owning ten percent or more of our common stock or to their associates, or to our affiliates.

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, 2016, 2015 and 2014, and the balance sheet data as of December 31, 2016 and 2015 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 period from December 16, 2013 (inception) through December 31, 2013 and the balance sheet data as of December 31, 2014 and 2013 is derived from our audited financial statements which are not included in this Annual Report on Form 10-K.

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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   |              |              | Period      |
|---|--|--------------|--------------|-------------|
|   | December 31,                                       |              |              | from        |
|   | 2016   | 2015         | 2014         | December    |
|   |  |              |              | 16, 2013    |
|   |  |              |              | (Inception) |
|   |  |              |              | through     |
|   |  |              |              | December    |
|   |  |              |              | 31, 2013    |
|   | (in thousands, except share and per share amounts) |              |              |             |
| <b>Consolidated Statements of Operations Data:</b>    |  |              |              |             |
| <b>Revenues:</b>                                      |  |              |              |             |
| Grant   | \$ 4,628   | \$ 6,085     | \$ —         | \$ —        |
| <b>Operating expenses:</b>                            |  |              |              |             |
| Research and development                              | \$ 18,143  | \$ 11,453    | \$ 6,830     | \$ 1,150    |
| General and administrative                            | 8,391  | 5,947        | 2,074        | 735         |
| Total operating expenses                              | 26,534   | 17,400       | 8,904        | 1,885       |
| Loss from operations                                  | (21,906 )  | (11,315 )    | (8,904 )     | (1,885 )    |
| <b>Other income (expense):</b>                        |  |              |              |             |
| Interest income                                       | 244  | 22           | 1            | -           |
| Change in fair value of forward sale contract         | —  | —            | (1,444 )     | (52 )       |
| Other expense, net                                    | (36 )  | (2 )         | —            | —           |
| Total other income (expense)                          | 208  | 20           | (1,443 )     | (52 )       |
| Net loss  | \$ (21,698 )                                       | \$ (11,295 ) | \$ (10,347 ) | \$ (1,937 ) |
| Deemed dividend to convertible preferred stockholders | —  | (228 )       | —            | —           |
| Net loss attributable to common stockholders and      |  |              |              |             |
| stockholders  | \$ (21,698 )                                       | \$ (11,523 ) | \$ (10,347 ) | \$ (1,937 ) |
| <b>Common Stock:</b>                                  |  |              |              |             |
| Basic and diluted net loss per share                  | \$ (2.22 )   | \$ (19.21 )  | \$ —         | \$ —        |
| Net loss attributable to common stockholders          | \$ (21,698 )                                       | \$ (11,523 ) | \$ —         | \$ —        |
| Basic and diluted weighted-average shares outstanding | 9,791,728  | 599,788      | —            | —           |
| <b>Class A-1 common:</b>                              |  |              |              |             |
| Basic and diluted net loss per share                  | \$ —   | \$ —         | \$ (20.13 )  | \$ (15.48 ) |
| Net loss attributable to class                        | \$ —   | \$ —         | \$ (3,321 )  | \$ (1,277 ) |
| Basic and diluted weighted-average shares outstanding | —  | —            | 165,000      | 82,500      |
| <b>Class A common:</b>                                |  |              |              |             |
| Basic and diluted net loss per share                  | \$ —   | \$ —         | \$ (17.06 )  | \$ (3.94 )  |
| Net loss attributable to class                        | \$ —   | \$ —         | \$ (5,706 )  | \$ (660 )   |
| Basic and diluted weighted-average shares outstanding | —  | —            | 334,522      | 167,261     |
| <b>Class B common:</b>                                |  |              |              |             |
| Basic and diluted net loss per share                  | \$ —   | \$ —         | \$ (40.17 )  | \$ —        |
| Net loss attributable to class                        | \$ —   | \$ —         | \$ (1,320 )  | \$ —        |
| Basic and diluted weighted-average shares outstanding | —  | —            | 32,861       | —           |

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|   | As of December 31, |          |          |         |
|---|--------------------|----------|----------|---------|
|   | 2016               | 2015     | 2014     | 2013    |
|   | (in thousands)     |          |          |         |
| <b>Consolidated Balance Sheet Data:</b>           |                    |          |          |         |
| Cash, cash equivalents, and marketable securities | \$63,502           | \$33,062 | \$2,616  | \$4,597 |
| Working capital                                   | 62,459             | 35,763   | 1,672    | 3,185   |
| Total assets                                      | 67,063             | 38,654   | 2,930    | 4,597   |
| Total liabilities                                 | 4,097              | 2,550    | 1,058    | 1,412   |
| Convertible preferred shares                      | —                  | 58,311   | 13,345   | 4,458   |
| Accumulated deficit                               | (45,277)           | (23,579) | (12,284) | (1,937) |
| Total members'/stockholders' equity (deficit)     | 62,966             | (22,207) | (11,473) | (1,273) |

## 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 committed to developing enzyme-based therapeutics in the field of amino acid metabolism to treat rare genetic diseases and cancer. Our engineered human enzymes are designed to degrade specific amino acids in the blood to target these diseases. In inborn errors of metabolism, or IEM, we are seeking to reduce the toxic levels of amino acids in patients to the normal range. In oncology, we are seeking to reduce amino acid blood levels below the normal range where we believe we will be able to exploit the dependence of certain cancers on specific amino acids.

Our lead product candidate, AEB1102, 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 I deficiency, an IEM, as well as some cancers which have shown to have a metabolic dependence on arginine. AEB1102 has demonstrated clinical proof-of-mechanism in both scenarios. In a Phase 1 clinical trial for the treatment of patients with Arginase I deficiency, a dose-proportional reduction in plasma arginine levels was observed in two patients. A reduction in blood arginine levels was also observed in Phase 1 clinical trials for the treatment of patients with advanced solid tumors and the hematological malignancies relapsed refractory acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS. These preliminary results support its potential use as a therapeutic of both Arginase I deficiency and certain cancers associated with abnormal amino acid metabolism.

We are conducting three clinical trials for AEB1102, consisting of one Phase 1/2 clinical trial for the treatment of Arginase I deficiency and two Phase 1 clinical trials for the treatment of certain cancers.

•**Arginase I deficiency.** Following completion of dosing for the first two adult patients in our Phase 1 clinical trial for the treatment of patients with Arginase I deficiency, we submitted a protocol amendment in November 2016 to broaden the scope of our Phase 1 trial into a Phase 1/2 trial. The amended protocol includes dosing of pediatric patients (two and older) and weekly repeat dosing, with the intent to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical response of AEB1102 in patients with this IEM. In the first quarter of 2017, we received IRB approval for the Phase 1/2 protocol for the treatment of patients with Arginase I deficiency at multiple clinical trial sites. In March 2017, we received an information request from the FDA which included comments and recommendations on the protocol amendment and a request for supporting documents based on their review of our completed toxicology studies, our dose escalation plan and our information to support the inclusion of pediatric patients. As recommended by the FDA, we replied with supporting information and requested a follow-up meeting. At this time, we believe our Phase 1/2 protocol provides an appropriate path to evaluate the safety and tolerability of AEB1102 in pediatric patients, and pending FDA feedback, we plan to initiate dosing in pediatric patients in the middle of 2017. In March 2017, we announced results from the first two adult patients in our Phase 1 clinical trial for the treatment of Arginase I deficiency at the 2017 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting, or ACMG Annual Meeting. We intend to continue enrollment of adult patients and plan to dose additional adult patients in the middle of 2017. Topline data from this trial is expected in the first half of 2018.

•**Advanced Solid Tumors.** In October 2015, we initiated enrollment for a Phase 1 dose escalation trial for cancer patients with advanced solid tumors. In this ongoing trial, AEB1102 was well-tolerated and patients have demonstrated a reduction in blood arginine levels, providing proof-of-mechanism. We expect to announce results of this Phase 1 dose escalation in patients with advanced solid tumors and anticipate initiating expansion arms in specific solid tumor types, potentially in combination with existing or emerging standards of care, in the fourth quarter of 2017 or the first quarter of 2018.

**Hematological Malignancies.** In July 2016, we initiated a Phase 1 clinical trial in patients the hematological malignancies AML and MDS in the United States and Canada. As demonstrated in the trial for patients with advanced solid tumors, the first three cohorts of this trial have demonstrated proof-of-mechanism. We expect to announce results of the Phase 1 dose escalation trial in patients with AML and MDS in the fourth quarter of 2017 or the first quarter of 2018.

We are also building a pipeline of additional product candidates targeting key amino acids and other metabolites, including homocystine, a target for another IEM as well as cysteine, and its oxidized form cystine, and methionine, for oncology indications.

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, completed on April 12, 2016, and collection of a research grant.

We have not recorded revenue from product sales and all of our revenue to date has been grant revenue. Since our inception, and through December 31, 2016, we have raised an aggregate of \$109.5 million to fund our operations through sale and issuance of convertible preferred and common equity securities and collected \$9.6 million in grant proceeds. As of December 31, 2016, we had cash, cash equivalents, and marketable securities of \$63.5 million.

We have incurred net losses in each year since inception. Our net losses were \$21.7 million, \$11.3 million, and \$10.3 million for the years ended December 31, 2016, 2015, and 2014, 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, 2016, we had an accumulated deficit of \$45.3 million. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and 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, AEB1102; concurrently develop our pipeline product candidates; expand and protect our intellectual property portfolio; and hire additional personnel. In addition, we have incurred and expect to continue to incur additional costs associated with operating as a public company.

## Components of Operating Results

### Revenue

To date, we have 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 covers a four year period from June 1, 2014 through May 31, 2018. The grant allows us to receive funds in advance of costs and allowable expenses being incurred. We record the revenue as qualifying costs are incurred and there is reasonable assurance that the conditions of the award have been met for collection. Proceeds received prior to the costs being incurred or the conditions of the award being met are recognized as deferred revenue until the services are performed and the conditions of the award are met.

On a quarterly basis, we are 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 result in the recognition of a grant receivable.





## 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 AEB1102. Since we currently do not have manufacturing capabilities and did not have an internal laboratory in 2016, we contracted with external providers for nonclinical studies, clinical trials and manufacturing services. Our research and development expenses include:

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

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;
- 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, 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, potential commercialization of our product candidates and the increased costs of operating as a public company. These increases will likely include incremental 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.

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#### Interest income

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

#### Loss on forward contract

The financing arrangement in connection with the sale and issuance of our Series A convertible preferred shares in December 2013 included a second closing in July 2014, which, for financial reporting purposes, resulted in a contract for the forward sale of an additional 837,594 Series A convertible preferred shares at a price of \$5.25 per share, contingent upon certain milestones being met. This freestanding financial instrument was classified as a liability because the underlying preferred shares are contingently redeemable. The forward sale contract was carried at fair value on the balance sheet, with changes in fair value recorded in earnings. The changes in fair value of the derivative liability from our inception through settlement in July 2014 were recorded as other income (expense) in the consolidated statements of operations.

#### Income taxes

Since inception in December 2013, through March 10, 2015, we were a Delaware LLC and elected to file as a partnership for federal and state income tax purposes through the year ended December 31, 2014. On March 10, 2015, we converted from a Delaware LLC to a Delaware corporation, and have subsequently filed a corporate income tax return for the year ended December 31, 2015. For tax purposes, we elected to be treated as a corporation under Subchapter C of Chapter 1 of the United States Internal Revenue Code, effective January 1, 2015. We therefore, were subject to federal and state tax expense beginning January 1, 2015.

We serve as a holding company for our seven wholly-owned subsidiary corporations and file consolidated corporate federal income tax returns. 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 management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of these financial statements requires us to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities as of the dates of the balance sheets and the reported amounts of expenses during the reporting periods. In accordance with GAAP, we base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances at the time such estimates are made. Actual results may differ materially from our estimates and judgments under different assumptions or conditions. We periodically review our estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates are reflected in our consolidated financial statements prospectively from the date of the change in estimate.

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.

#### Forward sale contract for Series A convertible preferred shares

In connection with the issuance of Series A convertible preferred shares on December 24, 2013, we entered into a contract for the forward sale of an additional 837,594 Series A convertible preferred shares at a price of \$5.25 per share, contingent upon certain milestones being met. This freestanding financial instrument was classified as a liability because the underlying preferred shares are contingently redeemable. The forward sale contract is carried at fair value on the balance sheet, with changes in fair value recorded in earnings. The liability was settled with the issuance of additional Series A convertible preferred shares on July 15, 2014.

We estimated the fair value of the forward sale contract for our Series A convertible preferred shares using a probability-weighted discount approach. The significant inputs used to estimate the fair value of the forward sale contract include the estimated present and future fair values of the Series A convertible preferred shares, the estimated probability of the milestone being achieved (initially 90%), the discount rate (20%) and an estimated time to the milestone event (initially estimated to be ten months).

#### Share/Stock-based compensation

We recognize the cost of share/stock-based awards granted to employees based on the estimated grant-date fair values of the awards. The value of the portion of the award that is ultimately expected to vest is recognized as expense ratably over the requisite service period. We recognize the compensation costs for awards that vest over several years on a straight-line basis over the vesting period. We recognize the cost of share/stock-based awards granted to nonemployees at their then-current fair values as services are performed, and are remeasured at each reporting date through the counterparty performance date.

Prior to March 2015, we operated as a Limited Liability Company, or LLC, and issued Common B incentive equity awards to employees, consultants and non-employee directors of the Company. In March 2015, upon conversion from a Delaware LLC to a Delaware corporation, the outstanding Common B share awards were converted into restricted common stock and options to purchase common stock, or collectively, the Replacement Awards.

We assessed the conversion of the Common B share awards as a modification under GAAP. Because there was no change in vesting timing or conditions and there was no incremental increase in the conversion date fair value as a result of the conversion, we allocated the original Common B share values to the restricted common stock and stock options proportionate to their conversion date fair values.

We estimate the grant date fair value of the non-Replacement Award 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:

- n 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).

n 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 until a sufficient amount of historical information regarding the volatility of our own stock price becomes available, or until circumstances change, such that the identified entities are no longer comparable companies. In the latter case, other suitable, similar entities whose share prices are publicly available would be utilized in the calculation.

n 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.

n 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.

In the year ended December 31, 2016, we elected to early adopt ASU No. 2016-09, Compensation - Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting, and began to account for forfeitures in compensation expense as they occur by reversing the previous compensation expense recognized. Previously, we estimated our forfeiture rate based on an analysis of our actual forfeitures and evaluated the adequacy of the forfeiture rate based on actual forfeiture experience, analysis of employee turnover behavior and other factors. The cumulative impact from any forfeiture rate adjustment would be recognized in the period of adjustment. We also considered the other areas of simplification included in this update, including income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows, and determined that they did not have an impact on the consolidated financial statements.

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 B awards and the common stock underlying option grants, our Board of Directors considered, among other things, timely valuations of our common shares and 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 B shares and common stock, including our stage of development; progress of our research and development efforts; the rights, preferences and privileges of our convertible preferred shares and preferred stock relative to those of our common shares and common stock; equity market conditions affecting comparable public companies and the lack of marketability of our common shares and 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, 2016 and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015, together with the changes in those items in dollars and as a percentage:

|                            | Year Ended             |            |            |        |
|----------------------------|------------------------|------------|------------|--------|
|                            | December 31,           |            | Dollar     | %      |
|                            | 2016                   | 2015       | Change     | Change |
|                            | (dollars in thousands) |            |            |        |
| <b>Revenues:</b>           |                        |            |            |        |
| Grant                      | \$4,628                | \$6,085    | \$(1,457 ) | -24 %  |
| <b>Operating expenses:</b> |                        |            |            |        |
| Research and development   | \$18,143               | \$11,453   | \$6,690    | 58 %   |
| General and administrative | 8,391                  | 5,947      | 2,444      | 41 %   |
| Total operating expenses   | 26,534                 | 17,400     | 9,134      | 52 %   |
| Loss from operations       | (21,906)               | (11,315)   | (10,591)   | 94 %   |
| Interest income            | 244                    | 22         | 222        | *      |
| Other expense, net         | (36 )                  | (2 )       | (34 )      | *      |
| Net loss                   | \$(21,698)             | \$(11,295) | \$(10,403) | 92 %   |

\*Percentage not meaningful

**Grant Revenues.** Grant revenues decreased by \$1.5 million, or 24%, to \$4.6 million for the year ended December 31, 2016 from \$6.1 million for the year ended December 31, 2015. The decrease was due to \$2.0 million in revenue for qualifying 2014 expenditures recognized in connection with the execution of the Grant Contract in June 2015. Upon execution of the Grant Contract, all accumulated qualified expenditures paid and incurred during the period from June 1, 2014 through June 30, 2015 were recognized as grant revenues in the year ended December 31, 2015. The decrease was offset by an increase in research and development costs associated with the clinical trials for AEB1102 in patients with advanced solid tumors and the hematological malignancies AML and MDS, for which we received grant revenue pursuant to the Grant Contract.

**Research and Development Expenses.** Research and development expenses increased by \$6.7 million, or 58%, to \$18.1 million for the year ended December 31, 2016 from \$11.5 million for the year ended December 31, 2015. Research and development expenses costs directly associated with our lead product candidate, AEB1102, increased to \$10.9 million for the year ended December 31, 2016 from \$7.0 million for the year ended December 31, 2015. The increase in research and development expenses was primarily due to:

- Higher nonclinical expenses, which increased by \$0.9 million as a result of additional toxicology studies and analysis costs in preparation for multi-dose clinical trials related to AEB1102 and additional research with the University of Texas at Austin, or the University;

- Higher personnel-related expenses, which increased by \$2.8 million as a result of additional employee headcount to expand our internal regulatory and clinical development capabilities in support of the three separate clinical trials for AEB1102 in patients with advanced solid tumors, Arginase I deficiency, and the hematological malignancies AML and MDS; and

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Higher clinical development expenses, which increased by \$3.0 million primarily as a result of initiating our Phase 1 dose escalation trials for AEB1102 in patients with advanced solid tumors in October 2015, Arginase I deficiency in June 2016, and the hematological malignancies AML and MDS in July 2016.

**General and Administrative Expenses.** General and administrative expenses increased by \$2.4 million, or 41%, to \$8.4 million for the year ended December 31, 2016 from \$5.9 million for the year ended December 31, 2015. The increase in general and administrative expenses was primarily due to an increase of \$0.8 million in employee compensation, recruiting, and travel expenses, \$0.8 million in professional services, audit and legal fees, and \$0.8 million in insurance and other administrative costs associated with being a public company.

**Interest Income.** Interest income consists of interest earned on our cash, cash equivalents, and marketable securities. The increase in interest income to \$244,000 for the year ended December 31, 2016 from \$22,000 for the year ended December 31, 2015 was primarily due to purchased cash equivalents and marketable securities in September 2015 and investment of funds received from our IPO in April 2016.

## Comparison of the Years Ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014, together with the changes in those items in dollars and as a percentage:

|   | Year Ended           |            | Dollar<br>Change | %<br>Change |
|---|----------------------|------------|------------------|-------------|
|   | December 31,<br>2015 | 2014       |                  |             |
| (dollars in thousands)                        |                      |            |                  |             |
| <b>Revenues:</b>                              |                      |            |                  |             |
| Grant   | \$6,085              | \$—        | \$6,085          | *           |
| <b>Operating expenses:</b>                    |                      |            |                  |             |
| Research and development                      | \$11,453             | \$6,830    | \$4,623          | 68 %        |
| General and administrative                    | 5,947                | 2,074      | 3,873            | 187 %       |
| Total operating expenses                      | 17,400               | 8,904      | 8,496            | 95 %        |
| Loss from operations                          | (11,315)             | (8,904)    | (2,411)          | 27 %        |
| Interest income                               | 22                   | 1          | 21               | *           |
| Change in fair value of forward sale contract | —                    | (1,444)    | 1,444            | *           |
| Other expense, net                            | (2)                  | —          | (2)              | *           |
| Net loss                                      | \$(11,295)           | \$(10,347) | \$(948)          | 9 %         |

\*Percentage not meaningful

**Grant Revenues.** We recorded grant revenues of \$6.1 million for the year ended December 31, 2015, including \$2.0 million in revenue for qualifying 2014 expenditures. Upon execution of the Grant Contract, all accumulated qualified expenditures paid and incurred during the period from June 1, 2014 through June 30, 2015 were recognized as grant revenues in the year ended December 31, 2015.

**Research and Development Expenses.** Research and development expenses increased by \$4.6 million, or 68%, to \$11.5 million for the year ended December 31, 2015 from \$6.8 million for the year ended December 31, 2014. Research and development expenses directly associated with our lead product candidate, AEB1102, increased to \$7.0 million for the year ended December 31, 2015 from \$3.7 million for the year ended December 31, 2014. The increase in research and development expenses was primarily due to:

- Higher nonclinical expenses, which increased by \$1.8 million as a result of additional biomarker-related costs in preparation for clinical trials related to AEB1102 and additional research with the University;
- Higher personnel-related expenses, which increased by \$1.3 million as a result of additional employee headcount in preparation for the initiation of clinical trials for AEB1102;
  - Higher clinical development expenses, which increased by \$0.8 million primarily as a result of initiating our Phase 1 dose escalation trial for AEB1102 in patients with advanced solid tumors in October 2015;
- Higher consulting expenses, which increased by \$0.4 million as a result of our additional nonclinical and clinical development efforts in 2015; and
- Higher clinical regulatory-related expenses, which increased by \$0.3 million as a result of expenses incurred in 2015 for the preparation and submission of two investigational new drug applications with the FDA for AEB1102 for the treatment of advanced solid tumors and Arginase I deficiency.

**General and Administrative Expenses.** General and administrative expenses increased by \$3.9 million, or 187%, to \$5.9 million for the year ended December 31, 2015 from \$2.1 million for the year ended December 31, 2014. The

increase in general and administrative expenses was primarily due to an increase of \$1.9 million in employee compensation, recruiting, and travel expenses and \$1.6 million in professional services, audit and legal fees associated with preparing to be a public company and the development of administrative functions. In addition, facility-related costs increased by \$0.3 million due to moving to a larger office in January 2015.

**Interest Income.** Interest income consists of interest earned on our cash, cash equivalents, and marketable securities. The increase in interest income to \$22,000 for the year ended December 31, 2015 from \$1,000 for the year ended December 31, 2014 was primarily due to funds invested from closing the Series B convertible preferred stock financing in March 2015.

## Liquidity and Capital Resources

## Sources of liquidity

We are an early stage biotechnology company with a limited operating history, and due to our significant research and development expenditures, we have generated operating losses since our inception and have not generated any revenue from the sale of any products. Since our inception and through December 31, 2016, we have funded our operations by raising an aggregate of \$109.5 million of gross proceeds from the sale and issuance of convertible preferred and common equity securities and collecting \$9.6 million in grant proceeds. Additionally, we entered into an agreement with a contract manufacturing organization, or CMO, in 2013 whereby we issued convertible preferred shares to the CMO in exchange for services performed, with the obligation fully satisfied in June 2015.

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 we expect to generate up to \$19.8 million in grant funding to fund our development of AEB1102. Through December 31, 2016, we have collected \$9.6 million in grant proceeds with \$10.2 million available for future collection under the grant contract. As of December 31, 2016, we have a grant receivable outstanding of \$1.2 million. 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, AEB1102. This includes both the research and development costs and the general and administrative expenses required to support those operations. Since we are an early stage 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 AEB1102 and expand our development efforts in our pipeline of nonclinical candidates.

As of December 31, 2016, we had available cash, cash equivalents, and marketable securities of \$63.5 million. Under our current operating plan, we believe that we have sufficient resources to fund our operations through March 31, 2019 with our existing cash, cash equivalents, and marketable securities.

## Cash flows

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

|  | Year Ended   |            |           |
|--|--------------|------------|-----------|
|  | December 31, |            |           |
|  | 2016         | 2015       | 2014      |
| Net cash (used in) provided by:                      |              |            |           |
| Operating activities                                 | \$(18,840)   | \$(10,982) | \$(7,335) |
| Investing activities                                 | (12,076)     | (4,014)    | (221)     |
| Financing activities                                 | 49,370       | 41,674     | 5,575     |
| Net increase (decrease) in cash and cash equivalents | \$18,454     | \$26,678   | \$(1,981) |

## Cash used in operating activities

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 operating activities for the year ended December 31, 2015 was \$11.0 million and reflected a net loss of \$11.3 million, offset in part by non-cash expenses of \$0.8 million for stock-based compensation and \$0.8 million for convertible preferred shares issued to a contract manufacturing organization in exchange for services performed. Cash used in operating activities also reflected an increase of \$1.7 million in grant accounts receivable from executing the Grant Contract in 2015 and \$0.6 million in prepaid expenses and other assets driven by prepaid research and development costs. The asset increases were offset, with cash provided by operating activities, by a \$1.1 million increase in accrued and other liabilities driven by additional accrued research and development costs, consulting, and legal accruals.

Cash used in operating activities for the year ended December 31, 2014 was \$7.3 million and reflected a net loss of \$10.3 million, offset in part by non-cash expenses of \$1.4 million for the change in fair value of the forward contracts associated with the second closing of the Series A financing, \$0.8 million for convertible preferred shares issued to a contract manufacturing organization in exchange for services performed, \$0.5 million for the discount on the sale of convertible preferred shares and \$0.1 million of share-based compensation.

#### Cash used in investing activities

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 used in investing activities for the year ended December 31, 2015 was \$4.0 million and primarily consisted of \$0.2 million in purchases of property and equipment and \$3.8 million in purchases of marketable securities.

Cash used in investing activities for the year ended December 31, 2014 was \$0.2 million and consisted primarily of capital purchases of computer and laboratory equipment.

#### Cash provided by financing activities

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.

Cash provided by financing activities for the year ended December 31, 2015 was \$41.7 million resulting from \$44.0 million from the closing of the Series B financing in March 2015, offset by \$0.3 million in Series B issuance costs and \$2.0 million in offering costs related to our IPO.

Cash provided by financing activities for the year ended December 31, 2014 was \$5.6 million, resulting from the second closing of the Series A financing in July 2014.

#### Future funding requirements and operational plan

Our operational plan for the near future is to continue clinical trials for our lead product candidate AEB1102 in three separate indications, Arginase I deficiency, advanced solid tumors, and the hematological malignancies AML and MDS, and to expand development for at least one additional product candidate. 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 AEB1102;
- funding the advancement of additional product candidates; and
- funding working capital, including general operating expenses.

We anticipate that we will continue to generate losses into the foreseeable future as we develop our lead 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 or debt facility or additional committed capital. To the extent that we raise additional equity, the ownership interest of our shareholders will be diluted.

Due to our significant research and development expenditures, we have generated substantial losses in each period since inception. We have an accumulated deficit of \$45.3 million as of December 31, 2016. We expect to incur substantial losses in the future as we expand our research and development capabilities. Based on those plans, we expect our existing cash, cash equivalent, and marketable securities will enable us to fund our operating expenses and capital expenditure requirements at least through March 31, 2019. 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.



## Contractual Obligations

The following table summarizes our contractual obligations as of December 31, 2016 (in thousands):

|                               | Payments Due by Period    |                    |                    |                            |
|-------------------------------|---------------------------|--------------------|--------------------|----------------------------|
|                               | Less<br>than<br>1<br>year | 1 to<br>3<br>years | 4 to<br>5<br>years | More<br>than<br>5<br>years |
| Operating leases              | \$262                     | \$574              | \$300              | \$ —                       |
| Sponsored research agreement  | 375                       | —                  | —                  | —                          |
| Total contractual obligations | \$637                     | \$574              | \$300              | \$ —                       |

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 is approximately \$1.1 million as of December 31, 2016.

In February 2017, we entered into a separate lease agreement for laboratory space in Austin, Texas, which will expire on December 31, 2017. The total estimated rent payments over the full term of the lease is approximately \$78,000.

In August 2016, we amended our sponsored research agreement with the University. The scope and term under the agreement were extended through August 31, 2017 with a \$750,000 increase in the maximum expenditure limitation. As of December 31, 2016, the research agreement, as amended, expires on August 31, 2017 with no remaining payment obligations after such date.

## 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 or products or services that are based upon, utilize, are developed from or materially incorporate the intellectual property resulting from the grant-funded activities for AEB1102. 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.

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 \$500,000 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, 2016, we do not have any off balance sheet arrangements, as defined by applicable SEC regulations.

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## 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 asset for leases with a lease-term of more than twelve months. The new standard is effective for fiscal years and interim periods beginning after December 15, 2018 and requires modified retrospective application. Early adoption is permitted. We are currently evaluating the impact that the adoption of ASU 2016-02 will have on our consolidated financial statements, but expect the impact to be limited to the operating lease agreement for office space in Austin, TX.

In March 2016, the FASB issued ASU No. 2016-09, Compensation - Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting. The standard is intended to simplify several areas of accounting for share-based compensation arrangements, including the income tax impact, classification of awards as either equity or liabilities, classification on the statement of cash flows and forfeitures. The standard is effective for fiscal years and interim periods beginning after December 15, 2016. Early adoption is permitted.

We elected to early adopt ASU 2016-09 for the three months ended December 31, 2016 using a modified retrospective approach, effective as if adopted the first day of the fiscal year January 1, 2016. We elected to account for forfeitures in compensation cost as they occur. The cumulative impact for the change in election was not material and was recognized in the year ended December 31, 2016. Additionally, we determined that none of the other provisions of ASU 2016-09 has a significant impact on its 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. These risks primarily include interest rate sensitivities.

As of December 31, 2016, we held \$63.5 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 and U.S. government and agency securities.

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 short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, an immediate 10% change in interest rates would not have a material effect on the fair market value of our 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.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

AEGLEA BIOTHERAPEUTICS, INC.

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Report of Independent Registered Public Accounting Firm

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

In our opinion, the accompanying consolidated balance sheets and the related consolidated statements of operations, comprehensive loss, changes in convertible preferred shares/stock and members'/stockholders' equity (deficit) and cash flows present fairly, in all material respects, the financial position of Aeglea BioTherapeutics, Inc. and its subsidiaries at December 31, 2016 and December 31, 2015, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2016 in conformity with accounting principles generally accepted in the United States of America. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP

Austin, Texas

March 23, 2017

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Aeglea BioTherapeutics, Inc.

## Consolidated Balance Sheets

(In thousands, except share and per share amounts)

|   | December 31,    |                 |
|---|-----------------|-----------------|
|   | 2016            | 2015            |
| <b>ASSETS</b>   |                 |                 |
| <b>CURRENT ASSETS</b>   |                 |                 |
| Cash and cash equivalents   | \$47,748        | \$29,294        |
| Marketable securities   | 15,754          | 3,768           |
| Restricted cash   | —               | 80              |
| Accounts receivable - grant   | 1,215           | 1,697           |
| Deferred offering costs   | —               | 2,535           |
| Prepaid expenses and other current assets   | 1,707           | 912             |
| <b>Total current assets</b>   | <b>66,424</b>   | <b>38,286</b>   |
| Property and equipment, net   | 599             | 348             |
| Other non-current assets  | 40              | 20              |
| <b>TOTAL ASSETS</b>   | <b>\$67,063</b> | <b>\$38,654</b> |
| <b>LIABILITIES, CONVERTIBLE PREFERRED STOCK, AND STOCKHOLDERS' EQUITY (DEFICIT)</b> |                 |                 |
| <b>CURRENT LIABILITIES</b>  |                 |                 |
| Accounts payable  | \$168           | \$176           |
| Deferred revenue  | 71              | —               |
| Accrued and other current liabilities   | 3,726           | 2,347           |
| <b>Total current liabilities</b>  | <b>3,965</b>    | <b>2,523</b>    |
| Other non-current liabilities   | 132             | 27              |
| <b>TOTAL LIABILITIES</b>  | <b>4,097</b>    | <b>2,550</b>    |
| <b>Commitments and Contingencies (Note 14 and 16)</b>                               |                 |                 |
| Series A convertible preferred stock, \$0.0001 par value; no shares and 2,172,524   |                 |                 |
| shares authorized as of December 31, 2016 and 2015, respectively; no shares         |                 |                 |
| and 2,172,520 shares issued and outstanding as of December 31, 2016 and             |                 |                 |
| 2015, respectively  | —               | 13,573          |
| Series B convertible preferred stock, \$0.0001 par value; no shares and 5,008,210   |                 |                 |
| shares authorized as of December 31, 2016 and 2015, respectively; no shares         |                 |                 |
| and 4,999,976 shares issued and outstanding as of December 31, 2016 and             |                 |                 |
| 2015, respectively  | —               | 44,738          |
| <b>STOCKHOLDERS' EQUITY (DEFICIT)</b>   |                 |                 |
| Preferred stock, \$0.0001 par value; 10,000,000 shares and no shares                | —               | —               |
| authorized as of December 31, 2016 and 2015, respectively;                          |                 |                 |
| no shares issued and outstanding as of December 31, 2016 and 2015,                  |                 |                 |

respectively

Common stock, \$0.0001 par value; 500,000,000 shares and 25,000,000

shares authorized as of December 31, 2016 and 2015, respectively;

13,430,833 shares and 757,336 shares issued and outstanding

as of December 31, 2016 and 2015, respectively

|   |           |          |
|---|-----------|----------|
|   | 1         | —        |
| Additional paid-in capital                          | 108,246   | 1,373    |
| Accumulated other comprehensive loss                | (4 )      | (1 )     |
| Accumulated deficit                                 | (45,277 ) | (23,579) |
| TOTAL STOCKHOLDERS' EQUITY (DEFICIT)                | 62,966    | (22,207) |
| TOTAL LIABILITIES, CONVERTIBLE PREFERRED STOCK, AND |           |          |
| STOCKHOLDERS' EQUITY (DEFICIT)                      | \$67,063  | \$38,654 |

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,<br>2016 | 2015        | 2014        |
| <b>Revenues:</b>  |                      |             |             |
| Grant   | \$4,628              | \$6,085     | \$—         |
| <b>Operating expenses:</b>                                    |                      |             |             |
| Research and development                                      | 18,143               | 11,453      | 6,830       |
| General and administrative                                    | 8,391                | 5,947       | 2,074       |
| Total operating expenses                                      | 26,534               | 17,400      | 8,904       |
| Loss from operations  | (21,906 )            | (11,315 )   | (8,904 )    |
| <b>Other income (expense):</b>                                |                      |             |             |
| Interest income   | 244                  | 22          | 1           |
| Change in fair value of forward sale contract                 | —                    | —           | (1,444 )    |
| Other expense, net  | (36 )                | (2 )        | —           |
| Total other income (expense)                                  | 208                  | 20          | (1,443 )    |
| Net loss  | \$(21,698 )          | \$(11,295 ) | \$(10,347 ) |
| Deemed dividend to convertible preferred stockholders         | —                    | (228 )      | —           |
| Net loss attributable to common shareholders and stockholders | \$(21,698 )          | \$(11,523 ) | \$(10,347 ) |
| <b>Common Stock:</b>  |                      |             |             |
| Basic and diluted net loss per share                          | \$(2.22 )            | \$(19.21 )  | \$—         |
| Net loss attributable to common stockholders                  | \$(21,698 )          | \$(11,523 ) | \$—         |
| Basic and diluted weighted-average shares outstanding         | 9,791,728            | 599,788     | —           |
| <b>Class A-1 common:</b>                                      |                      |             |             |
| Basic and diluted net loss per share                          | \$—                  | \$—         | \$(20.13 )  |
| Net loss attributable to class                                | \$—                  | \$—         | \$(3,321 )  |
| Basic and diluted weighted-average shares outstanding         | —                    | —           | 165,000     |
| <b>Class A common:</b>  |                      |             |             |
| Basic and diluted net loss per share                          | \$—                  | \$—         | \$(17.06 )  |
| Net loss attributable to class                                | \$—                  | \$—         | \$(5,706 )  |
| Basic and diluted weighted-average shares outstanding         | —                    | —           | 334,522     |
| <b>Class B common:</b>  |                      |             |             |
| Basic and diluted net loss per share                          | \$—                  | \$—         | \$(40.17 )  |
| Net loss attributable to class                                | \$—                  | \$—         | \$(1,320 )  |
| Basic and diluted weighted-average shares outstanding         | —                    | —           | 32,861      |

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, |            |            |
|  | 2016         | 2015       | 2014       |
| Net loss                                 | \$(21,698)   | \$(11,295) | \$(10,347) |
| Other comprehensive loss:                |              |            |            |
| Unrealized loss on marketable securities | (3 )         | (1 )       | —          |
| Total comprehensive loss                 | \$(21,701)   | \$(11,296) | \$(10,347) |

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

Aeglea BioTherapeutics, Inc.

Consolidated Statements of Changes in Convertible Preferred Shares/Stock and Members’/Stockholders’ Equity (Deficit)

(In thousands)

|           | Series A<br>Convertible<br>Preferred |         | Series A<br>Convertible<br>Preferred |        | Series B<br>Convertible<br>Preferred |        | Common<br>A-1 |        | Common A |        | Common B |        | Common |        | Additional | Accumulated | Other |
|-----------|--------------------------------------|---------|--------------------------------------|--------|--------------------------------------|--------|---------------|--------|----------|--------|----------|--------|--------|--------|------------|-------------|-------|
|           | Shares                               | Amount  | Shares                               | Amount | Shares                               | Amount | Shares        | Amount | Shares   | Amount | Shares   | Amount | Shares | Amount | Capital    | Deficit     | Loss  |
| December  | 972                                  | \$4,458 | —                                    | \$—    | —                                    | \$—    | 165           | \$277  | 335      | \$387  | —        | \$—    | —      | \$—    | \$—        | \$(1,937)   | \$—   |
| Series    |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| ble       |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| shares    |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| n         |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| velopment | 133                                  | 845     | —                                    | —      | —                                    | —      | —             | —      | —        | —      | —        | —      | —      | —      | —          | —           | —     |
| Series    |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| ble       |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| shares    |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| r cash,   |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| in        |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| costs     | 1,068                                | 5,575   | —                                    | —      | —                                    | —      | —             | —      | —        | —      | —        | —      | —      | —      | —          | —           | —     |
| on        | —                                    | 1,936   | —                                    | —      | —                                    | —      | —             | —      | —        | —      | —        | —      | —      | —      | —          | —           | —     |
| e         |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| of        |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |
| ble       |                                      |         |                                      |        |                                      |        |               |        |          |        |          |        |        |        |            |             |       |

|          |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
|----------|---------|----------|-------|--------|-------|--------|-------|-------|-------|-------|-------|-------|-----|---|----------|---|
| Series   |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| able     |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
|          | —       | 531      | —     | —      | —     | —      | —     | —     | —     | —     | —     | —     | —   | — | —        | — |
| d        |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| ion      | —       | —        | —     | —      | —     | —      | —     | —     | —     | —     | 355   | 147   | —   | — | —        | — |
|          | —       | —        | —     | —      | —     | —      | —     | —     | —     | —     | —     | —     | —   | — | (10,347) | — |
| December | 2,173   | 13,345   | —     | —      | —     | —      | 165   | 277   | 335   | 387   | 355   | 147   | —   | — | (12,284) | — |
| of       |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| 3 shares | —       | —        | —     | —      | —     | —      | —     | —     | —     | —     | (1 )  | —     | —   | — | —        | — |
| d        |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| ion      |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| ision    |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| LC to    |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| on       | —       | —        | —     | —      | —     | —      | —     | —     | —     | —     | —     | 20    | —   | — | —        | — |
| n from   |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| on       | (2,173) | (13,345) | 2,173 | 13,345 | —     | —      | (165) | (277) | (335) | (387) | (354) | (167) | 753 | — | 831      | — |
| ividend  |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| able     |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| lers     |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| ersion   |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| LC to    |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| n        | —       | —        | —     | 228    | —     | —      | —     | —     | —     | —     | —     | —     | —   | — | (228)    | — |
| f Series |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| able     |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| stock    |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| et of    |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| ssuance  | —       | —        | —     | —      | 4,930 | 43,679 | —     | —     | —     | —     | —     | —     | —   | — | —        | — |
| f Series | —       | —        | —     | —      | 70    | 1,059  | —     | —     | —     | —     | —     | —     | —   | — | —        | — |
| able     |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| stock    |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |
| n        |         |          |       |        |       |        |       |       |       |       |       |       |     |   |          |   |

Development

and

operation after

operation from

operation

of stock

of stock

loss on

of stock

of stock

December

|   |     |       |          |       |          |   |     |   |     |   |     |   |     |     |     |          |            |       |
|---|-----|-------|----------|-------|----------|---|-----|---|-----|---|-----|---|-----|-----|-----|----------|------------|-------|
| — | —   | —     | —        | —     | —        | — | —   | — | —   | — | —   | — | —   | —   | 747 | —        | —          |       |
| — | —   | —     | —        | —     | —        | — | —   | — | —   | — | —   | — | 4   | —   | 23  | —        | —          |       |
| — | —   | —     | —        | —     | —        | — | —   | — | —   | — | —   | — | —   | —   | —   | —        | (1)        |       |
| — | —   | —     | —        | —     | —        | — | —   | — | —   | — | —   | — | —   | —   | —   | (11,295) | —          |       |
| — | \$— | 2,173 | \$13,573 | 5,000 | \$44,738 | — | \$— | — | \$— | — | \$— | — | \$— | 757 | \$— | \$1,373  | \$(23,579) | \$(1) |

Aeglea BioTherapeutics, Inc.

Consolidated Statements of Changes in Convertible Preferred Shares/Stock and Members'/Stockholders' Equity  
(Deficit) (continued)

(In thousands)

|  | Series A    |           | Series B    |           | Common |        |        |        | Additional | Accumulated | Other         | Total         |
|--|-------------|-----------|-------------|-----------|--------|--------|--------|--------|------------|-------------|---------------|---------------|
|  | Convertible | Preferred | Convertible | Preferred | A-1    | A      | B      | Common |            |             |               |               |
|  | Shares      | Amount    | Shares      | Amount    | Shares | Shares | Shares | Stock  | Paid-in    | Deficit     | Comprehensive | Stockholders' |
|  | Amount      | Amount    | Amount      | Amount    | Amount | Amount | Amount | Amount | Capital    | Loss        | Income        | Equity        |
| Balances—December 31, 2015   | —           | \$ 2,173  | —           | \$ 13,573 | 5,000  | —      | —      | \$ 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  | —      | 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  | —           | —         | —           | —         | —      | —      | —      | —      | —          | —           | (3)           | (3)           |

| securities        |     |     |   |     |   |     |     |     |          |           |            |       |          |
|-------------------|-----|-----|---|-----|---|-----|-----|-----|----------|-----------|------------|-------|----------|
| Net loss          | —   | —   | — | —   | — | —   | —   | —   | —        | (21,698)  | (21,698)   |       |          |
| Balances—December |     |     |   |     |   |     |     |     |          |           |            |       |          |
| 31, 2016          | \$— | \$— | — | \$— | — | \$— | \$— | \$— | \$13,431 | \$108,246 | \$(45,277) | \$(4) | \$62,966 |

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,  |               |                 |
|   | 2016          | 2015          | 2014            |
| <b>CASH FLOWS FROM OPERATING ACTIVITIES</b>                                     |               |               |                 |
| Net loss  | \$(21,698)    | \$(11,295)    | \$(10,347)      |
| Adjustments to reconcile net loss to net cash used in operating activities:     |               |               |                 |
| Depreciation and amortization   | 132           | 89            | 19              |
| Purchase premium on marketable securities                                       | (146 )        | (5 )          | —               |
| Amortization of premium on marketable securities                                | 101           | 2             | —               |
| Deferred rent   | 12            | 4             | —               |
| Amortization of lease allowance liability                                       | (22 )         | (23 )         | —               |
| Share/stock-based compensation  | 1,221         | 767           | 147             |
| Change in fair value of forward sale contract                                   | —             | —             | 1,444           |
| Discount on Series A convertible preferred shares                               | —             | —             | 531             |
| Research and development services settled with convertible preferred<br>stock   | 110           | 812           | 845             |
| Changes in operating assets and liabilities:                                    |               |               |                 |
| Accounts receivable - grant   | 482           | (1,697 )      | —               |
| Prepaid expenses and other assets   | (924 )        | (586 )        | (112 )          |
| Accounts payable  | (8 )          | (169 )        | (165 )          |
| Deferred revenue  | 71            | —             | —               |
| Accrued and other liabilities   | 1,829         | 1,119         | 303             |
| Net cash used in operating activities   | (18,840)      | (10,982)      | (7,335 )        |
| <b>CASH FLOWS FROM INVESTING ACTIVITIES</b>                                     |               |               |                 |
| Purchases of property and equipment   | (212 )        | (208 )        | (181 )          |
| Purchases of marketable securities  | (20,390)      | (3,766 )      | —               |
| Proceeds from maturities of marketable securities                               | 8,446         | —             | —               |
| Decrease (increase) in restricted cash  | 80            | (40 )         | (40 )           |
| Net cash used in investing activities   | (12,076)      | (4,014 )      | (221 )          |
| <b>CASH FLOWS FROM FINANCING ACTIVITIES</b>                                     |               |               |                 |
| Proceeds from issuance of convertible preferred stock, net of offering<br>costs |               |               |                 |
|   | —             | 43,679        | 5,575           |
| Proceeds from initial public offering, net of (payments of) offering costs      | 49,294        | (2,028 )      | —               |
| Proceeds from employee stock plan purchases and issuance of common<br>stock     |               |               |                 |
|   | 76            | 23            | —               |
| Net cash provided by financing activities                                       | 49,370        | 41,674        | 5,575           |
| <b>NET INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS</b>                     | <b>18,454</b> | <b>26,678</b> | <b>(1,981 )</b> |
| <b>CASH AND CASH EQUIVALENTS</b>  |               |               |                 |
| Beginning of period   | 29,294        | 2,616         | 4,597           |

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|   |          |          |         |
|---|----------|----------|---------|
| End of period   | \$47,748 | \$29,294 | \$2,616 |
| Supplemental Disclosure of Non-Cash Investing and Financing Information:                                  |          |          |         |
| Unpaid amounts related to purchase of property and equipment  | \$172    | \$—      | \$—     |
| Deemed dividend to Series A convertible preferred stockholders upon conversion from an LLC to corporation | \$—      | \$228    | \$—     |
| Convertible preferred stock issued for research and development services to be performed                  | \$—      | \$232    | \$—     |
| 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 | \$—      | \$—     |
| Settlement of the forward sale contract for Series A convertible preferred shares                         | \$—      | \$—      | \$1,936 |

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



Aeglea BioTherapeutics, Inc.

Notes to Consolidated Financial Statements

## 1. The Company and Basis of Presentation

Aeglea BioTherapeutics, Inc. (“Aeglea” or the “Company”) is a clinical-stage biotechnology company committed to developing enzyme-based therapeutics in the field of amino acid metabolism to treat 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 (“Aeglea LLC”) and was converted from a Delaware LLC to a Delaware corporation (the “LLC Conversion”) on March 10, 2015. The LLC Conversion was effective January 1, 2015 for tax purposes and as such, the Company filed a consolidated tax return for the full year ended December 31, 2015. The Company operates in one segment and has its principal offices in Austin, Texas.

### Initial Public Offering

On April 6, 2016, the Company’s Registration Statement on Form S-1 (File No. 333-205001) relating to the initial public offering (“IPO”) of its common stock was declared effective by the Securities and Exchange Commission (“SEC”). The IPO closed on April 12, 2016, and 5,481,940 shares of common stock were sold 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.

Immediately prior to the closing of the IPO, all shares of outstanding convertible preferred stock were automatically converted, at a ratio of one share of common stock for each share of convertible preferred stock, into 7,172,496 shares of common stock with the related carrying value of \$58.3 million reclassified to common stock and additional paid-in capital.

In connection with the IPO, the Company amended its Restated Certificate of Incorporation (the “Public Certificate”) 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. There are no shares of preferred stock outstanding as of December 31, 2016.

### Reverse Stock Split

The Company’s Board of Directors and stockholders approved a 1-for-10.5 reverse stock split of the Company’s common stock and preferred stock. The reverse stock split became effective on March 28, 2016 upon filing an amended Restated Certificate of Incorporation (the “Split Certificate”). The Split Certificate remained in effect until closing of the IPO, at which time the company amended the Restated Certificate of Incorporation and filed the Public Certificate.

All share and per share amounts in the consolidated financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital.

### Liquidity

As of December 31, 2016, the Company had working capital of \$62.5 million, an accumulated deficit of \$45.3 million, and cash, cash equivalents, and marketable securities of \$63.5 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 research, 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 plan, the Company believes that it has sufficient resources to fund operations through March 31, 2019 with its existing cash, cash equivalents, and marketable securities. The Company will need to secure additional funding in the future, in order to carry out all of its planned research and development activities. If the Company is unable to obtain additional financing or generate license or product revenue, the lack of liquidity could have a material adverse effect on the Company's future prospects.

#### Basis of Presentation

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

## 2. Summary of Significant Accounting Policies

#### Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Such management estimates include those related to accruals of research and development related costs, fair values of preferred and common shares and preferred and common stock, a forward sale contract, share/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 shares, common stock, and the forward sale contract for Series A convertible preferred shares. The board of directors determined the estimated fair value of common shares and 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 shares, the superior rights and preferences of securities senior to the Company's common shares and 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 shares, common stock, and the forward sale contract for Series A convertible preferred shares (see Notes 6, 9, and 11).

#### 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. Unrealized gains and losses are excluded from earnings and are reported as a component of accumulated other 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, 2016, 2015, and 2014. Interest on

marketable securities is included in interest income.

#### Restricted Cash

Restricted cash consisted of a money market account held by a financial institution as collateral for the Company's obligations under a corporate credit card agreement. In September 2016, the collateral requirement was terminated and the restricted cash balance was recorded as cash and cash equivalents.

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### 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 FDIC insured bank obligations, 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.

### Deferred Offering Costs

Deferred offering costs, which primarily consists of direct incremental legal, printing, and accounting fees relating to the Company's IPO of its common stock, are capitalized. At the closing of the IPO, the deferred offering costs were offset against the proceeds from the IPO and recorded to additional paid-in capital.

### 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, 2016, 2015, and 2014.

### 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 a lease agreement for its office facilities. The lease is classified as an operating lease. The Company records rent expense on a straight-line basis over the term of the lease 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 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.

#### Convertible Preferred Stock

The Company recorded the issuance of all convertible preferred stock net of offering costs on the dates of issuance, which represented the carrying value. The conversion feature of the convertible preferred stock was subject to certain anti-dilution provisions, which if triggered, would have required the Company to seek shareholder approval to increase the number of shares of common stock authorized. In the event that the Company could not deliver the conversion shares because it did not have an adequate number of common stock authorized, the convertible preferred stock would have been redeemable. Accordingly, the Company classified the convertible preferred stock in temporary equity. The Company did not adjust the carrying value of the convertible preferred stock to their redemption values,

since it was uncertain whether or when a redemption event would occur. The convertible preferred stock outstanding was automatically converted into shares of common stock immediately prior to the completion of the IPO in April 2016 (see Note 1).



## Forward Sale Contract for Series A Convertible Preferred Shares

In connection with the issuance of Series A convertible preferred shares on December 24, 2013, the Company entered into a contract for the forward sale of an additional 837,594 Series A convertible preferred shares at a price of \$5.25 per share, contingent upon certain milestones being met. This freestanding financial instrument was classified as a liability because the underlying preferred shares were contingently redeemable. The forward sale contract was carried at fair value on the balance sheet, with changes in fair value recorded in earnings. The liability was settled with the issuance of additional Series A convertible preferred shares on July 15, 2014 (see Note 6).

## Revenue Recognition

The Company's sole source of revenue is 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 is recognized when qualifying costs are incurred and there is reasonable assurance that the conditions of the award have been met for collection. Proceeds received prior to the costs being incurred or the conditions of the award being met are recognized as deferred revenue until the services are performed and the conditions of the award are 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, share/stock-based compensation, consulting costs, contract research service costs, laboratory supplies, 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. In June 2015, 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.

## Share/Stock-Based Compensation

The Company recognizes the cost of share/stock-based awards granted to employees based on the estimated grant-date fair values of the awards. The value of the portion of the award that is ultimately expected to vest is recognized as expense ratably over the requisite service period. The Company recognizes the compensation costs for awards that vest over several years on a straight-line basis over the vesting period. The Company recognizes the cost of share/stock-based awards granted to nonemployees at their then-current fair values as services are performed, and are remeasured at each reporting date through the counterparty performance date.

## Income Taxes

Effective January 1, 2015, the Company, for tax purposes, converted from a partnership to a corporation and continues to serve as a holding company for seven wholly-owned subsidiary corporations. Beginning with the year ended December 31, 2015, the Company filed a consolidated corporate federal income tax return. The Company and its subsidiaries 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 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 (deficit) from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company's other comprehensive 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 asset for leases with a lease-term of more than twelve months. The new standard is effective for fiscal years and interim periods beginning after December 15, 2018 and requires modified retrospective application. Early adoption is permitted. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements, but expect the impact to be limited to the operating lease agreement for office space in Austin, TX.

In March 2016, the FASB issued ASU No. 2016-09, Compensation - Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting. The standard is intended to simplify several areas of accounting for share-based compensation arrangements, including the income tax impact, classification of awards as either equity or liabilities, classification on the statement of cash flows and forfeitures. The standard is effective for fiscal years and interim periods beginning after December 15, 2016. Early adoption is permitted.

The Company elected to early adopt ASU 2016-09 for the three months ended December 31, 2016 using a modified retrospective approach, effective as if adopted the first day of the fiscal year January 1, 2016. The Company elected to account for forfeitures in compensation cost as they occur. The cumulative impact for the change in election was not material and was recognized in the year ended December 31, 2016. Additionally, the Company determined that none of the other provisions of ASU 2016-09 has a significant impact on its consolidated financial statements.

### 3. Cash Equivalents and Marketable Securities

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

|                               | December 31, 2016 |                     |                      | Estimated<br>Fair<br>Value |
|-------------------------------|-------------------|---------------------|----------------------|----------------------------|
|                               | Amortized<br>Cost | Unrealized<br>Gains | Unrealized<br>Losses |                            |
| Cash equivalents:             |                   |                     |                      |                            |
| Money market funds            | \$4,584           | \$ —                | \$ —                 | \$ 4,584                   |
| Reverse repurchase agreements | 39,250            | —                   | —                    | 39,250                     |

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|                                     |          |      |         |           |
|-------------------------------------|----------|------|---------|-----------|
| Total cash equivalents              | 43,834   | —    | —       | 43,834    |
| Marketable securities:              |          |      |         |           |
| US government and agency securities | 15,758   | —    | (4 )    | 15,754    |
| Total marketable securities         | \$15,758 | \$ — | \$ (4 ) | \$ 15,754 |

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|                                     | December 31, 2015 |            | Gross<br>Unrealized<br>Losses | Estimated<br>Fair<br>Value |
|-------------------------------------|-------------------|------------|-------------------------------|----------------------------|
|                                     | Amortized         | Unrealized |                               |                            |
|                                     | Cost              | Gains      |                               |                            |
| <b>Cash equivalents:</b>            |                   |            |                               |                            |
| Money market funds                  | \$3,988           | \$ —       | \$ —                          | \$ 3,988                   |
| Reverse repurchase agreements       | 16,250            | —          | —                             | 16,250                     |
| Total cash equivalents              | 20,238            | —          | —                             | 20,238                     |
| <b>Marketable securities:</b>       |                   |            |                               |                            |
| US government and agency securities | 3,769             | —          | (1 )                          | 3,768                      |
| Total marketable securities         | \$3,769           | \$ —       | \$ (1 )                       | \$ 3,768                   |

The reverse repurchase agreements are settled in cash nightly, and as such are classified as cash equivalents. All of the cash equivalents and marketable securities held as of December 31, 2016 and 2015 had maturities of less than one year.

As of December 31, 2016 and 2015, the Company held nine and five debt securities, respectively, that were in an unrealized loss position for less than one year. The aggregate fair value of debt securities in an unrealized loss position as of December 31, 2016 and 2015 were \$15.8 million and \$2.5 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, 2016 and 2015.

#### 4. Property and Equipment, Net

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

|   | December 31, |       |
|---|--------------|-------|
|   | 2016         | 2015  |
| Laboratory equipment                            | \$221        | \$138 |
| Furniture and office equipment                  | 202          | 118   |
| Computer equipment                              | 102          | 79    |
| Software  | 44           | 44    |
| Leasehold improvements                          | 270          | 77    |
| Property and equipment, gross                   | 839          | 456   |
| Less: Accumulated depreciation and amortization | (240)        | (108) |
| Property and equipment, net                     | \$599        | \$348 |

Depreciation and amortization expense for the years ended December 31, 2016, 2015, and 2014 was \$132,000, \$89,000, and \$19,000, respectively. All of the Company's long-lived assets are located in the United States.

## 5. Accrued and Other Current Liabilities

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

|   | December 31, |         |
|---|--------------|---------|
|   | 2016         | 2015    |
| Accrued compensation                              | \$1,270      | \$571   |
| Accrued contracted research and development costs | 1,749        | 863     |
| Accrued professional and consulting fees          | 480          | 863     |
| Accrued and other current liabilities             | 227          | 50      |
| Total accrued and other current liabilities       | \$3,726      | \$2,347 |

## 6. Convertible Preferred Stock

On December 24, 2013, the Company raised \$5.1 million through the issuance of 971,928 Series A convertible preferred shares at \$5.25 per share. The financing arrangement included a contract for the forward sale of an additional 837,594 Series A convertible preferred shares at a price of \$5.25 per share, contingent upon certain milestones being met. This freestanding financial instrument was classified as a liability because the underlying preferred share were contingently redeemable. The fair value of the forward sale contract at issuance was \$440,000. The fair value of the forward sale contract at settlement on July 15, 2014 was \$1.9 million.

The change in fair value of the derivative liability was recorded as Other Income (Expense) in the consolidated statements of operations. For the year ended December 31, 2014, the Company recognized \$1.4 million in expense due to changes in fair value of the derivative liability. The forward sale contract was settled on July 15, 2014 when the Company issued and received payment for additional Series A convertible preferred shares, and the fair value of the financial instrument on that date was reclassified to Series A convertible preferred shares.

On July 15, 2014, the Company raised \$5.6 million through the issuance of 1,067,592 Series A convertible preferred shares at \$5.25 per share (including 837,594 convertible preferred shares related to the forward sale contract). The Series A convertible preferred shares issued on July 15, 2014 were recorded at their fair value of \$7.56 per share (see Note 11). The Company recognized \$531,000 in expense for the 229,998 Series A convertible preferred shares that were not covered by the forward sale contract and were issued to an investor providing sponsored research and employees of the company at a discount. The expense was primarily recorded as research and development expense because the counterparties were engaged in such activities on behalf of the Company (see Note 14).

On March 10, 2015, the Company converted from a Delaware limited liability company into a Delaware corporation and changed the Company's name from Aeglea BioTherapeutics Holdings, LLC to Aeglea BioTherapeutics, Inc. In connection with the LLC Conversion, all of the Company's outstanding common shares and convertible preferred shares were converted into shares of common stock and convertible preferred stock. Further, the outstanding Common B share awards were converted into a combination of vested and unvested restricted common stock and vested and unvested stock options with no changes to the vesting provisions (see Note 9). Upon the LLC Conversion, each then-outstanding Series A convertible preferred share was converted into one share of Series A convertible preferred stock, par value \$0.0001 per share. The Company determined that the LLC Conversion resulted in a deemed dividend from stockholders of common stock to stockholders of Series A convertible preferred stock of \$0.11 per share of Series A convertible preferred stock. The Company recorded \$228,000 as an increase in the carrying amount of the Series A convertible preferred stock and as a reduction of additional paid-in capital. Such dividend was determined by comparing the fair value of the Series A convertible preferred shares immediately prior to the conversion to the fair value of the Series A convertible preferred stock issued in the conversion.

Also on March 10, 2015, the Company issued 4,929,948 shares of Series B convertible preferred stock, par value \$0.0001 per share, at an issuance price equal to \$8.93 per share and received gross proceeds of \$44.0 million. In connection with the financing, the Company incurred total offering costs of \$321,000.

On April 12, 2016, immediately prior to the closing of the IPO, all of the Company's outstanding convertible preferred stock was automatically converted into an aggregate total of 7,172,496 shares of common stock (see Note 1). As of December 31, 2016, there were no shares of preferred stock outstanding.

Convertible preferred stock consisted of the following as of December 31, 2015 (in thousands, except share amounts):

| December 31, 2015 |           |             |                 |
|-------------------|-----------|-------------|-----------------|
| Preferred         | Preferred | Liquidation | Carrying Common |

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|                                      | Stock      | Stock       | Preference | Value     | Stock      |
|--------------------------------------|------------|-------------|------------|-----------|------------|
|                                      | Authorized | Issued and  |            |           | Issuable   |
|                                      |            | Outstanding |            |           | Upon       |
|                                      |            |             |            |           | Conversion |
| Series A convertible preferred stock | 2,172,524  | 2,172,520   | \$ 11,406  | \$ 13,573 | 2,172,520  |
| Series B convertible preferred stock | 5,008,210  | 4,999,976   | \$ 44,625  | \$ 44,738 | 4,999,976  |



Prior to the closing of the IPO, the holders of convertible preferred stock had various rights, privileges, and preferences as follows:

#### Conversion

Each share of convertible preferred stock was convertible at any time and at the option of the holder into that number of fully-paid and non-assessable common stock determined by dividing the original issue price of the convertible preferred stock by the conversion price in effect on the date of conversion (a 1:1 ratio at the time of the conversion).

The convertible preferred stock was automatically convertible into shares of common stock at the then-current conversion rate upon (i) a vote of 62% of the outstanding Series B convertible preferred stock, or (ii) the closing of a firm commitment underwritten public offering that met aggregate gross proceed and pricing terms.

The respective applicable conversion price was subject to adjustment upon any future stock splits or stock combinations, reclassifications or exchanges of similar stock, upon a reorganization, merger or consolidation of the Company, upon the issuance or sale by the Company of common stock for consideration less than the applicable conversion price, or upon the issuance of any share purchase rights that are exercisable at a strike price less than the applicable conversion price.

#### Dividends

Each share of convertible preferred stock was entitled to non-cumulative dividends of 8% of the original issue price per share, per annum, if, as and when declared by the Board of Directors. Dividends to Series A and Series B stockholders were to be paid in advance of any distributions to common stockholders. No dividends were declared prior to the conversion of the shares into common stock upon the closing of the IPO.

#### Voting

Each share of convertible preferred stock had voting rights equal to an equivalent number of shares of common stock into which it was convertible and voted together as one class along with the common stock. The holders of convertible preferred stock had the right to vote on all significant matters as to which holders of common stock had the right to vote.

For as long as at least 342,857 shares of any series of convertible preferred stock (subject to adjustment in the event of a recapitalization affecting the convertible preferred stock) remained outstanding, the Company had to obtain the affirmative vote or written consent by at least 62% of the then-outstanding Series B convertible preferred stock along with Board consent to consummate significant transactions including, but not limited to, the authorization and issuance of additional shares or share classes, amending the certificate of incorporation, and the approval of a deemed liquidation event.

#### Liquidation

In the event of any liquidation, dissolution, or winding up of the Company, either voluntary or involuntary, the holders of the Series A and Series B convertible preferred stock were entitled to be paid out of the assets of the Company an amount per share equal to \$5.25 and \$8.93 respectively, prior to and in preference to any distribution to the holders of common stock.

If assets were insufficient to make payments in full to all holders of Series A and Series B convertible preferred stock, then the assets or consideration would be distributed ratably among the convertible preferred stockholders. Prior to the LLC Conversion, distributions were determined based upon the distribution preferences in the LLC agreement discussed further below. Subsequent to the LLC Conversion, remaining assets would be distributed among the holders

of convertible preferred stock and holders of common stock on pro rata basis based on the number of shares held, treating all shares of preferred stock as if they had been converted to common stock pursuant to the then-applicable conversion terms.

#### LLC Distributions

Prior to the LLC Conversion, the holders of the Series A convertible preferred shares were entitled to receive distributions out of any assets legally available, prior and in preference to any distributions to Common A-1, Common A, and Common B shares, up to the preference amount that equals the original issue price of \$5.25 per share adjusted for share splits, share distributions, combinations and reclassifications.

After the payment of the preference amount to holders of Series A convertible preferred shares, any remaining amount would be paid to the holders of the Series A convertible preferred shares and Common A-1 shares on a pro rata basis; until the Company had distributed an aggregate of \$1.0 million to the Common A-1 shares. Any remaining amount would be paid to the holders of Series A convertible preferred shares and Common A shares on a pro rata basis; until the Company had distributed to Common A shares an aggregate amount equal to the amount Common A-1 shares received.

Thereafter, if assets remained in the Company, they would be paid to the holders of the Series A convertible preferred shares, Common A-1 shares, Common A shares and Common B shares on a per share pro rata basis; provided that with respect to all Common B shares having a threshold amount, no distribution would be paid with respect to such Common shares until the aggregate amount of all distributions exceeded the threshold amount. All Common B Shares were issued with an applicable Threshold Amount set by the Board of Directors to qualify the shares as “profits interest” within the meaning of Revenue Procedure 93-27 as clarified by Revenue Procedure 2001-43.

To the extent that the amounts available for distribution were insufficient to pay the full amounts to which holders of the shares would otherwise be entitled, the holders of such shares entitled to receive distributions should share ratably in any such distribution in proportion to the respective amounts that would otherwise be payable.

No distributions were declared or paid by the Company prior to the LLC Conversion.

#### Redemption

The Series A and Series B convertible preferred stock were not mandatorily redeemable as they did not have a set redemption date or date after which the stock could be redeemed by the holders. However, the stock was contingently redeemable upon a deemed liquidation event and the trigger of certain anti-dilution provisions upon conversion to common stock without an adequate number of authorized common stock.

#### 7. Common Stock

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, 2016, no common stock dividends had been declared by the board of directors.

The Company’s former LLC Agreement authorized Aeglea LLC to issue three classes of common shares, each with no par value: Common A-1 shares, Common A shares, and Common B shares. Upon the LLC Conversion, each outstanding Common A-1 and Common A share was automatically converted into one share of common stock, par value \$0.0001 per share. See Note 9 regarding the conversion of outstanding Common B shares.

#### 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 covers 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 in royalties.

The agreement includes reimbursement for qualified expenditures incurred and recognized in 2014. Upon execution of the Grant Contract, grant revenue was recognized for the accumulated qualified expenditures paid and recognized in the period from June 1, 2014 through June 30, 2015. For the years ended December 31, 2016, 2015, and 2014 the Company recognized \$4.6 million, \$6.1 million, and \$0, respectively, in grant revenues for qualified expenditures under the grant. As of December 31, 2016 and 2015, the Company had an outstanding grant receivable of \$1.2 million and \$1.7 million, respectively, for the grant expenditures that were paid but had not been reimbursed and deferred revenue of \$71,000 and \$0, respectively, for proceeds received but the costs had not been incurred or the conditions of the award had not been met.

## 9. Share/Stock-Based Compensation

### 2013 Equity Incentive Plan

In 2013, the Company adopted the 2013 Equity Incentive Plan (“2013 Plan”). The 2013 Plan provides incentives to employees, consultants and non-employee directors of the Company by providing incentive awards of Common B shares or any other class of equity authorized by the Company and designated by the Board of Directors as incentive equity. The Company classified the incentive awards as equity-classified grants of unvested stock within the scope of ASC 718.

The Common B shares were issued upon grant date and held in escrow in the grantee’s name, subject to vesting requirements. Unvested shares could participate in any distributions allocated to the Common B shares and would remain in the custody of the Company until vesting occurred, at which time the funds would be released and voting rights commenced.

Prior to the LLC Conversion and for the year ended December 31, 2014, the Company granted 355,156 Common B shares with a weighted average grant date fair value of \$1.66 per share.

Upon the LLC Conversion, the Company terminated the 2013 Plan and adopted the 2015 Equity Incentive Plan (“2015 Plan”). All Common B shares issued under the 2013 Plan were replaced with stock options and restricted stock issued under the 2015 Plan.

### Modification of Common B Share Awards

As discussed in Note 6, in connection with the LLC Conversion on March 10, 2015, the 355,156 Common B share awards granted, less forfeitures of 1,474 shares, were converted into a combination of 253,232 vested and unvested shares of restricted common stock and 100,446 vested and unvested options to purchase common stock (collectively the “Replacement Awards”) with no changes to the vesting provisions. The conversion ratio for each award was dependent upon the issuance date of the relevant shares with the modification affecting seven employees.

In accordance with ASC 718, the Company determined the fair value of the Common B share awards held by employees and nonemployees immediately before the Replacement Awards were issued and compared that amount to the then fair value of the Replacement Awards. Given there was no incremental fair value in connection with the issuance of the Replacement Awards, the Company continues to recognize the compensation expense originally estimated for the Common B shares at the date of grant. The original Common B share values were allocated to stock options and restricted stock awards based on proportionate conversion date fair values.

### 2015 Equity Incentive Plan

The 2015 Plan, administered by the Board of Directors, 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, 2016, a total of 699,573 shares of common stock are subject to options outstanding under the 2015 Plan and 75,932 shares of unvested restricted stock are outstanding under the 2015 Plan. The shares will become available under the 2016 Equity Incentive Plan (“2016 Plan”) to the extent the options are forfeited or lapse unexercised or the restricted stock is forfeited prior to vesting.

#### 2016 Equity Incentive Plan

On April 5, 2016, the day preceding the effectiveness of the Registration Statement, the 2016 Plan became effective 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.

As of December 31, 2016, the total number of shares reserved for issuance under the 2016 Plan was 1,624,561, of which 447,362 shares were subject to outstanding option awards.

The 2016 Plan allows the Company's board of directors to approve an annual increase in the number of shares available for issuance thereunder, to be added on the first day of each fiscal year, beginning on January 1, 2017 and continuing through 2023, up to 4% of the outstanding number of shares of the Company's common stock on the December 31 immediately prior to the date of increase. As a result of the operation of this provision, on January 1, 2017, an additional 537,233 shares became available for issuance under the 2016 Plan.

The Company generally grants stock-based awards with service conditions only ("service-based" awards). Awards granted under the 2016 Plan and 2015 Plan generally vest over four or five years and expire after ten years, although awards have been granted with vesting terms less than four years.

#### 2016 Employee Stock Purchase Plan

On April 6, 2016, upon the effectiveness of the Registration Statement, the 2016 Employee Stock Purchase Plan ("2016 ESPP") became effective. 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. For the year ended December 31, 2016, the Company issued and sold 19,061 shares under the 2016 ESPP. The remaining 145,939 shares are available for issuance as of December 31, 2016.

#### Modification of Stock Options

In May 2016, the Company's board of directors approved the modification of 542,392 outstanding stock options for 21 employees to align the vesting schedule of existing awards with the Company's planned vesting schedule for future awards. The result was an acceleration of vesting for the modified awards. Stock options with a five year vesting schedule and 25% vesting after year two and 6.25% quarterly thereafter were modified to a four year vesting schedule with 25% vesting after year one and 2.08% monthly thereafter. Stock options with a four year vesting schedule and 25% vesting after year one and 6.25% quarterly thereafter were modified to a similar four year vesting schedule with 25% vesting after year one and 2.08% monthly thereafter. The modified awards have service conditions only.

In accordance with ASC 718, the Company determined the fair value of the awards immediately before the modification and compared that amount to the then-fair value of the modified awards. Given there was no incremental fair value in connection with the modification of the awards, the Company will continue to recognize the compensation expense originally estimated for the stock options at the date of grant over the modified service period. The Company recognized \$89,000 in cumulative expense as of the modification date related to changes in the service period for the modified awards.

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The following table summarizes employee and nonemployee stock option activity for the year ended December 31, 2016:

|   | Shares     | Weighted Average | Weighted Average   | Aggregate               |
|---|------------|------------------|--------------------|-------------------------|
|   | Under      | Exercise         | Contractual        | Intrinsic               |
|   | Options    | Price            | Term<br>(in years) | Value<br>(in thousands) |
| Outstanding as of December 31, 2015         | 629,848    | \$ 4.55          | 9.29               | \$ 2,833                |
| Granted                                     | 731,779    | 7.04             |                    |                         |
| Exercised                                   | —          | —                |                    |                         |
| Forfeited                                   | (214,692 ) | 7.19             |                    |                         |
| Outstanding as of December 31, 2016         | 1,146,935  | \$ 5.64          | 8.64               | \$ 440                  |
| Options vested and expected to vest         |            |                  |                    |                         |
| as of December 31, 2016                     | 1,137,407  | \$ 5.66          | 8.64               | \$ 431                  |
| Options exercisable as of December 31, 2016 | 390,033    | \$ 5.07          | 8.35               | \$ 213                  |

For the years ended December 31, 2016 and 2015, the weighted-average grant date fair value of non-replacement award options granted was \$7.04 and \$3.48, respectively. There were no option exercises during the year ended December 31, 2016. The total intrinsic value of options exercised during the year ended December 31, 2015 was \$25,000.

There were no stock options issued to or vested for non-employees during the year ended December 31, 2016. For the year ended December 31, 2015, the Company issued 25,387 stock options to non-employees with 11,279 options vesting in the period.

#### Restricted Common Stock

As part of the LLC Conversion, the Company granted restricted common stock 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 Company issued 253,232 restricted stock awards (“RSAs”) during the year ended December 31, 2015 and all are Replacement Awards from the conversion of the Common B share awards as discussed above. The Company allocated the fair value from the Common B shares to the restricted stock at the then-applicable conversion date fair value.

The following table summarizes employee and nonemployee restricted stock activity for the year ended December 31, 2016:



|  | Weighted  |         |
|--|-----------|---------|
|  | Average   |         |
|  | Grant     |         |
|  | Date Fair |         |
|  | Shares    | Value   |
| Unvested restricted common stock as of December 31, 2015 | 118,554   | \$ 1.85 |
| Granted  | —         | —       |
| Vested   | (42,622 ) | 1.86    |
| Forfeited  | —         | —       |
| Unvested restricted common stock as of December 31, 2016 | 75,932    | \$ 1.96 |

The fair value of RSAs that vested during the years ended December 31, 2016 and 2015 was \$258,000 and \$933,000, respectively.

There were no RSAs granted to non-employees during the year ended December 31, 2016. The Company issued 61,096 RSAs to non-employees during the year ended December 31, 2015 (and as part of the LLC Conversion) with 32,588 RSAs vesting in the period.

## Share/Stock-Based Compensation Expense

Total share/stock-based compensation expense recognized from the Company's equity incentive plans and the 2016 ESPP for the years ended December 31, 2016, 2015, and 2014 was as follows (in thousands):

|   | Year Ended           |               |          |               |          |               |
|---|----------------------|---------------|----------|---------------|----------|---------------|
|   | December 31,<br>2016 |               | 2015     |               | 2014     |               |
|   | Employee             | Non-Employees | Employee | Non-Employees | Employee | Non-Employees |
| Research and development                        | \$389                | \$ —          | \$101    | \$ 340        | \$7      | \$ 30         |
| General and administrative                      | 832                  | —             | 326      | —             | 107      | 3             |
| Total share/stock-based<br>compensation expense | \$1,221              | \$ —          | \$427    | \$ 340        | \$114    | \$ 33         |

No related tax benefits were recognized for the years ended December 31, 2016, 2015, and 2014.

The non-employee awards contain both performance and service-based vesting conditions. No expense was recognized for the unvested non-employee awards with only a performance condition for the years ended December 31, 2016, 2015, and 2014. The performance-based vesting conditions represent counterparty performance conditions. Share/stock-based compensation expense is recognized if the performance condition is considered probable of achievement using management's best estimates. The lowest potential aggregate fair values of the unvested awards were \$0 as of and for the years ended December 31, 2016, 2015, and 2014.

As of December 31, 2016, the Company had an aggregate of \$3.1 million and \$89,000 of unrecognized stock-based compensation expense for options and RSAs outstanding, respectively, which is expected to be recognized over a weighted average period of 2.6 years and 1.1 years, respectively.

In determining the fair value of the non-Replacement Award 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. 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 similar entities until a sufficient amount of historical information regarding the volatility of the Company's own share price becomes available or until circumstances change, such that the identified entities are no longer comparable companies. In the latter case, other suitable, similar entities whose share prices are publicly available would be utilized in the calculation.

#### 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 non-Replacement Award stock options granted under the 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,<br>2016 | 2015   |
| 2016 Plan and 2015 Plan |                      |        |
| Expected term           | 5.99                 | 6.29   |
| Expected volatility     | 87 %                 | 87 %   |
| Risk-free interest      | 1.28 %               | 1.37 % |
| Dividend yield          | 0 %                  | 0 %    |
| 2016 ESPP               |                      |        |
| Expected term           | 0.45                 | —      |
| Expected volatility     | 82 %                 | —      |
| Risk-free interest      | 0.50 %               | —      |
| Dividend yield          | 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 year ended December 31, 2016, the Company provided \$51,000 in contributions to the plan. The Company did not provide any contributions during the years ended December 31, 2015 or 2014.

## 11. 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, 2016 |          |            | Total    |
|-------------------------------------|-------------------|----------|------------|----------|
|                                     | Level<br>1        | Level 2  | Level<br>3 |          |
| Financial Assets                    |                   |          |            |          |
| Money market funds                  | \$4,584           | \$—      | \$ —       | \$4,584  |
| Reverse repurchase agreements       | —                 | 39,250   | —          | 39,250   |
| US government and agency securities | —                 | 15,754   | —          | 15,754   |
| Total financial assets              | \$4,584           | \$55,004 | \$ —       | \$59,588 |

|                                     | December 31, 2015 |                 |             |                 |
|-------------------------------------|-------------------|-----------------|-------------|-----------------|
|                                     | Level             |                 | Level       | Total           |
|                                     | 1                 | Level 2         | 3           |                 |
| <b>Financial Assets</b>             |                   |                 |             |                 |
| Money market funds                  | \$3,988           | \$—             | \$ —        | \$3,988         |
| Reverse repurchase agreements       | —                 | 16,250          | —           | 16,250          |
| US government and agency securities | —                 | 3,768           | —           | 3,768           |
| <b>Total financial assets</b>       | <b>\$3,988</b>    | <b>\$20,018</b> | <b>\$ —</b> | <b>\$24,006</b> |

The Company measures the fair value of money market funds on quoted prices in active markets for identical asset or liabilities. The Level 2 assets include reverse repurchase agreements and U.S. government and agency 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.

The liability for the forward sale contract is considered a Level 3 instrument. The forward sale contract was settled on July 15, 2014 when the Company issued and received payment for additional Series A convertible preferred shares, and the fair value of the financial instrument of \$1.9 million was reclassified to Series A convertible preferred shares.

#### 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.

The fair value of the forward sale contract for Series A convertible preferred shares was measured using a probability-weighted discount approach. Inputs used to determine estimated fair value of the forward sale contract include the estimated present and future fair values of the Series A convertible preferred shares, the estimated probability of the milestone being achieved (initially 90%), the discount rate (20%), and an estimated time to the milestone event (initially estimated to be ten months). Increases or decreases in the discount rate generally would result in a directionally opposite impact to the fair value measurement of this forward sale contract. Changes in the estimated fair value of the Series A convertible preferred shares generally would result in a directionally similar impact on the fair value measurement of the forward sale contract.

#### 12. Income Taxes

For the years ended December 31, 2016, 2015, and 2014, 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,

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|   | 2016      | 2015      | 2014      |
|---|-----------|-----------|-----------|
| Tax provision derived by applying the federal statutory |           |           |           |
| rate to income before income taxes                      | \$(7,377) | \$(3,841) | \$(3,518) |
| Permanent differences and other                         | 333       | 307       | 54        |
| Federal tax credits                                     | (1,921)   | (321)     | (289)     |
| State tax credits                                       | (404)     | —         | —         |
| Losses of LLC entity attributable to the members        | —         | —         | 730       |
| Conversion of LLC from partnership to corporation       | —         | (21)      | —         |
| Change in the valuation allowance                       | 9,369     | 3,876     | 3,023     |
| Income tax expense /(benefit)                           | \$—       | \$—       | \$—       |

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

|                                       | December 31,    |                |
|---------------------------------------|-----------------|----------------|
|                                       | 2016            | 2015           |
| <b>Deferred tax assets</b>            |                 |                |
| Net operating loss carryforward       | \$12,286        | \$6,336        |
| Intangible assets                     | 38              | 41             |
| Accrued expense                       | 335             | 184            |
| Stock-based compensation              | 283             | 112            |
| Federal tax credits                   | 3,291           | 624            |
| State tax credits                     | 404             |                |
| Other                                 | 76              | 36             |
| <b>Total deferred tax assets</b>      | <b>16,713</b>   | <b>7,333</b>   |
| <b>Deferred tax liabilities</b>       |                 |                |
| Depreciable assets                    | \$(60 )         | \$(49 )        |
| <b>Total deferred tax liabilities</b> | <b>(60 )</b>    | <b>(49 )</b>   |
| <b>Less: Valuation allowance</b>      | <b>(16,653)</b> | <b>(7,284)</b> |
| <b>Deferred tax assets, net</b>       | <b>\$—</b>      | <b>\$—</b>     |

The Company has established a valuation allowance equal to the net deferred tax asset 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 approximately \$9.4 million, \$3.9 million, and \$3.0 million during the years ended December 31, 2016, 2015, and 2014, respectively, primarily due to continuing loss from operations.

As of December 31, 2016 and 2015, the Company had U.S. net operating loss carryforwards ("NOL") of approximately \$36.1 million and \$18.6 million, respectively. As of December 31, 2016 and 2015, the Company had U.S. tax credit carryforwards of approximately \$3.3 million and \$624,000, respectively, and state tax credit carryforwards of approximately \$612,000 and \$0, respectively. The net operating loss and tax credit carryforwards will begin to expire in 2033, if not utilized. The net operating loss carryforwards are subject to Internal Revenue Service adjustments until the statute closes on the year the net operating loss is utilized.

The Company has not completed a study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since the Company's formation due to the complexity and cost associated with such a study, and the fact that there may be additional such ownership changes in the future. If the Company has experienced an ownership change at any time since its formation, utilization of the NOL or R&D credit carryforwards would be subject to an annual limitation under Section 382 or 383 of the Internal Revenue Code, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term, tax-exempt rate, and then could be subject to additional adjustments, as required. Additionally, the separate return limitation year ("SRLY") rules may apply to losses of the Company's seven wholly-owned 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 2013 and subsequent years.

13. Net Loss Per Share Attributable to Common Shareholders and Stockholders

The Company computed net loss attributable per common shareholder and 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 6). The Company considered convertible preferred shares/stock to be participating securities. In the event that the Company had paid out distributions, holders of convertible preferred shares/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 each class of common share, 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 shares/stock did not have an obligation to fund losses and are therefore excluded from the calculation of basic net loss per share. Starting in the first quarter of 2015 in connection with the LLC Conversion, the Company's Series A and B convertible preferred stock were entitled to receive noncumulative dividends and in preference to any dividends on shares of the Company's common stock.

Basic and diluted net loss per share attributable to common shareholders and stockholders is computed by dividing net loss attributable to the applicable class of common share and common stock by the weighted-average number of that class of common share and common stock outstanding during the period. For net loss per share attributable to common stockholders for the year ended December 31, 2015, the effect of the LLC Conversion is presented prospectively from January 1, 2015 as none of the losses for the year ended December 31, 2015 were allocated to the members of Aeglea LLC. 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. Additionally, the convertible preferred stock dividend is included in the loss attributable to common stockholders.

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,<br>2016 | 2015      | 2014      |
| Series A convertible preferred shares/stock                     | 611,392              | 2,172,520 | 1,557,870 |
| Series B convertible preferred stock                            | 1,407,097            | 4,047,734 | —         |
| Unvested restricted common stock                                | 100,634              | 153,355   | —         |
| Options to purchase common stock                                | 1,063,778            | 450,458   | —         |
| Forward sale contract for Series A convertible preferred shares | —                    | —         | 447,482   |
| Unvested Class B common shares                                  | —                    | —         | 151,936   |

#### 14. Research and License Agreements

##### Contract Research Agreement

In December 2013, the Company entered into a contract research agreement with a contract manufacturing organization ("CMO") under which the CMO provides research and development services to the Company in exchange for cash and convertible preferred shares.

For the year ended December 31, 2016, no shares were issued to the CMO. For the years ended December 31, 2015 and 2014, the Company issued 70,028 Series B convertible preferred shares and 133,000 Series A convertible preferred shares to the CMO, respectively, with fair values of \$1.1 million and \$845,000, respectively. The number of convertible preferred shares contractually issuable to the counterparty was determined by dividing a fixed monetary amount by the issuance-date fair value of the issued shares. These services are expensed as research and development costs in accordance with the fair value of the consideration paid and as the services are rendered.

The Company was obligated to issue a variable number of shares of convertible preferred stock upon the completion of certain milestones related to the research and development of the Company's products. In June 2015, the contract

research agreement was amended to convert the remaining unmet milestone awards from share-based payments to cash. As of December 31, 2016 and 2015, all related obligations payable in convertible preferred stock under the agreement have been satisfied.

#### University Research Agreement

In December 2013, the Company entered into a research agreement with the University of Texas at Austin (the “University”). 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 therapies.

Under the research agreement, the Company was required to pay the University an annual amount not to exceed \$386,000 during the one-year term of the agreement from the effective date. Pursuant to subsequent amendments to the

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research agreement, the term and maximum expenditure limitation were extended and increased through August 31, 2017 for a combined \$1.8 million, including an amendment in August 2016 which increased the maximum expenditure limitation by \$750,000 for additional research to be performed by the University. For the years ended December 31, 2016, 2015, and 2014, the Company paid \$832,000, \$563,000, and \$386,000, respectively, to the University under the research agreement.

#### 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 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.

For the year ended December 31, 2016, the Company paid \$5,000 in annual license fees for each license agreement. For the years ended December 31, 2015 and 2014, there were no license fees due or paid. 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. See Note 17 regarding the terms of the Restated License.

#### 15. Related Party Transactions

The spouse of the Company's Chief Executive Officer provided consulting services to the Company. For the years ended December 31, 2016, 2015, and 2014, the Company paid \$399,000, \$433,000, and \$146,000, respectively, to the spouse in consulting fees, which were recorded in Research and Development expenses. As of December 31, 2016, the Company had no outstanding liability to the related party. As of December 31, 2015, the Company had an outstanding liability of \$129,000.

One of the founders, 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 57,142 Common B shares (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. For the years ended December 31, 2016, 2015, and 2014, the Company paid \$50,000 in each year, respectively, to the Founder under the consulting agreement. As of December 31, 2016 and 2015, the Company had no outstanding liability to the related party.

#### 16. Commitments and Contingencies

The Company leases office space in Austin, TX under an operating lease that commenced in January 2015. The lease was amended in September 2016 to increase office space and extend the term to December 31, 2020. In addition, the amended lease provides for tenant improvement allowances on both the original space and expansion space totaling \$200,000. As provided in the lease amendment, 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 the lease.

Under the terms of the amended office lease agreement, the security deposit requirement was set at \$39,000 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):

|                              |         |
|------------------------------|---------|
| 2017                         | \$262   |
| 2018                         | 283     |
| 2019                         | 291     |
| 2020                         | 300     |
| Thereafter                   | —       |
| Total minimum lease payments | \$1,136 |

For the years ended December 31, 2016, 2015, and 2014, the Company incurred \$151,000, \$140,000, and \$17,000 in rent expense under non-cancellable operating leases.

In August 2016, the Company amended the research agreement with the University to further extend the period of performance and increase the limitation of funding to perform additional research. Under the terms of the amendment, the performance period was extended to August 31, 2017 with a remaining \$375,000 expected to be paid in 2017 (see Note 14).

#### 17. Subsequent Events

On January 31, 2017, the Company and the University entered into the Restated License. The Company may be required to pay the University up to \$6.4 million 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 \$500,000 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 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.

#### 18. Selected Quarterly Financial Data (Unaudited)

Selected quarterly results from operations for the years ended December 31, 2016 and 2015 are as follows (in thousands, except per share amounts):

|   | 2016 Quarter Ended |           |               |              |
|---|--------------------|-----------|---------------|--------------|
|   | March 31,          | June 30,  | September 30, | December 31, |
| Grant revenues                              | \$859              | \$1,373   | \$ 1,149      | \$ 1,247     |
| Loss from operations                        | (4,567)            | (5,495)   | (6,301 )      | (5,543 )     |
| Net loss                                    | (4,547)            | (5,430)   | (6,238 )      | (5,483 )     |
| Basic and diluted net loss per common share | \$(7.10 )          | \$(0.46 ) | \$ (0.47 )    | \$ (0.41 )   |

|   | 2015 Quarter Ended |           |               |              |
|---|--------------------|-----------|---------------|--------------|
|   | March 31,          | June 30,  | September 30, | December 31, |
| Grant revenues                              | \$—                | \$3,427   | \$ 1,073      | \$ 1,585     |
| Loss from operations                        | (2,469)            | (1,432)   | (3,417 )      | (3,997 )     |
| Net loss                                    | (2,468)            | (1,427)   | (3,413 )      | (3,987 )     |
| Basic and diluted net loss per common share | \$(4.71 )          | \$(2.44 ) | \$ (5.57 )    | \$ (6.36 )   |

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, 2016, 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

This Annual Report on Form 10-K does not include a report of management’s assessment regarding internal control over financial reporting or an attestation report of our registered public accounting firm due to a transition period established by the rules of the SEC for newly public companies. Additionally, 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, 2016 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated herein by reference to our Proxy Statement with respect to our 2017 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 2017 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 2017 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 2017 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 2017 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.



PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

The following documents are filed as part of this report:

1. Financial Statements

See Index to Financial Statements at Item 8 herein.

2. Financial Statement Schedules

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

3. Exhibits

See the Exhibit Index immediately following the signature page of this report.

ITEM 16. FORM 10-K SUMMARY

None.

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## 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 23, 2017

## AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ David G. Lowe, Ph.D.  
David G. Lowe, 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 David G. Lowe, 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.

| Signature  | Title   | Date           |
|--|---|----------------|
| /s/ David G. Lowe, Ph.D.<br>David G. Lowe, Ph.D.     | President, Chief Executive Officer and Director<br>(Principal Executive Officer)                                | March 23, 2017 |
| /s/ Charles N. York II<br>Charles N. York II         | Chief Financial Officer and Vice President<br>(Principal Accounting Officer and<br>Principal Financial Officer) | March 23, 2017 |
| /s/ Russell J. Cox<br>Russell J. Cox                 | Director  | March 23, 2017 |
| /s/ George Georgiou, Ph.D.<br>George Georgiou, Ph.D. | Director  | March 23, 2017 |
| /s/ Sandesh Mahatme, LLM<br>Sandesh Mahatme, LLM     | Director  | March 23, 2017 |
| /s/ Anthony G. Quinn, M.B Ch.B, Ph.D.                | Director  | March 23, 2017 |

Anthony G. Quinn, M.B Ch.B, Ph.D.

/s/ Armen Shanafelt, Ph.D.  
Armen Shanafelt, Ph.D.

Director

March 23, 2017

/s/ Suzanne Bruhn, Ph.D.  
Suzanne Bruhn, Ph.D.

Director

March 23, 2017

## EXHIBIT INDEX

| Exhibit Number | Description of Document   | Incorporate by Reference |            |                | Exhibit Filed No. | Filed Herewith |
|----------------|---|--------------------------|------------|----------------|-------------------|----------------|
|                |   | Form                     | File No.   | Date of Filing |                   |                |
| 3.1*           | Restated Certificate of Incorporation   | S-1/A                    | 333-205001 | 9/14/2015      | 3.2               |                |
| 3.4*           | Restated Bylaws   | S-1/A                    | 333-205001 | 9/14/2015      | 3.5               |                |
| 4.1*           | Form of Common Stock Certificate.   | S-1/A                    | 333-205001 | 9/14/2015      | 4.1               |                |
| 4.2*           | Amended and Restated Investors' Rights Agreement, dated March 10, 2015, by and among the Registrant and certain of its stockholders, as amended.  | S-1                      | 333-205001 | 6/16/2015      | 4.2               |                |
| 10.1*          | Form of Indemnification Agreement.  | S-1/A                    | 333-205001 | 9/14/2015      | 10.1              |                |
| 10.2*†         | 2015 Equity Incentive Plan and forms of award agreements.   | S-1                      | 333-205001 | 6/16/2015      | 10.2              |                |
| 10.3*†         | 2016 Equity Incentive Plan and forms of award agreements.   | S-1/A                    | 333-205001 | 3/28/2016      | 10.3              |                |
| 10.4*†         | 2016 Employee Stock Purchase Plan and forms of award agreements.  | S-1/A                    | 333-205001 | 3/28/2016      | 10.3              |                |
| 10.5*†         | Form of Stock Restriction Agreement.  | S-1                      | 333-205001 | 6/16/2015      | 10.5              |                |
| 10.6*†         | Executive Employment Agreement, dated July 7, 2015, by and between the Registrant and Dr. David G. Lowe.  | S-1/A                    | 333-205001 | 9/14/2015      | 10.6              |                |
| 10.7*†         | Offer Letter, dated December 28, 2013, issued by the Registrant to Dr. Scott W. Rowlinson.  | S-1/A                    | 333-205001 | 9/14/2015      | 10.7              |                |
| 10.8*†         | Sponsored Research Agreement No. UTA13-001113, dated December 24, 2013, between The University of Texas at Austin ("UT-Austin") and Aeglea BioTherapeutics, Inc., Aeglea Development Company, Inc., AERase, Inc., AEMase, Inc., AECase, Inc., AE4ase, Inc., AE5ase, Inc. and AE6ase., Inc., as amended. | 10-Q                     | 001-37722  | 11/9/2016      | 10.2              |                |
| 10.9*†         | Master Services Agreement, dated December 24, 2013, between KBI Biopharma, Inc. Aeglea Development Company, Inc. and the Registrant and First Amendment to Master Services Agreement, dated June 30, 2015, between KBI Biopharma, Inc., Aeglea Development Company, Inc. and Registrant.                | S-1/A                    | 333-205001 | 9/14/2015      | 10.10             |                |

10.10\* Office Lease, dated November 24, 2014, between Barton  
Oaks Office Center, LLC and the Registrant. S-1 333-205001 6/16/2015 10.11  
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Edgar Filing: Aeglea BioTherapeutics, Inc. - Form 10-K

| Exhibit Number | Description of Document   | Incorporate by Reference |            |                | Exhibit Filed No. | Filed Herewith |
|----------------|---|--------------------------|------------|----------------|-------------------|----------------|
|                |   | Form                     | File No.   | Date of Filing |                   |                |
| 10.11*         | First Amendment to Office Lease and Assignment and Assumption of Lease dated September 20, 2016 to Office Lease dated November 24, 2014, between Barton Oaks Office Center, LLC, Aeglea Development Company, Inc., and Aeglea BioTherapeutics, Inc. | 10-Q                     | 001-37722  | 11/9/2016      | 10.1              |                |
| 10.12*‡        | Consulting Agreement, dated February 18, 2014, by and between the Registrant and George Georgiou.   | S-1                      | 333-205001 | 6/16/2015      | 10.12             |                |
| 10.13#         | 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                               |                          |            |                |                   | X              |
| 10.14*†        | Cancer Research Grant Contract, dated June 15, 2015, between AERase, Inc. and the Cancer Prevention Research Institute of Texas.  | S-1                      | 333-205001 | 6/16/2015      | 10.15             |                |
| 10.15*‡        | CEO Severance Agreement, dated July 7, 2015, by and between the Registrant and Dr. David G. Lowe.   | S-1/A                    | 333-205001 | 9/14/2015      | 10.16             |                |
| 10.16*‡        | Vice President Severance Agreement dated July 10, 2015 by and between Registrant and Dr. Scott W. Rowlinson.  | S-1/A                    | 333-205001 | 9/14/2015      | 10.17             |                |
| 10.17*‡        | Offer Letter, dated May 4, 2015, issued by the Registrant to Mr. Henry Hebel.   | S-1/A                    | 333-205001 | 3/14/2016      | 10.17             |                |
| 10.18*‡        | Vice President Severance Agreement dated January 14, 2016 by and between Registrant and Mr. Henry Hebel.  | S-1/A                    | 333-205001 | 3/14/2016      | 10.18             |                |
| 10.19‡         | Offer Letter, dated June 16, 2014, issued by the Registrant to Mr. Charles N. York II.  |                          |            |                |                   | X              |
| 10.20‡         | Vice President of Finance Severance Agreement dated July 7, 2015 by and between Registrant and Mr. Charles N. York II.  |                          |            |                |                   | X              |
| 21.1*          | Subsidiaries of the Registrant.   | S-1                      | 333-205001 | 6/16/2015      | 21.1              |                |
| 23.1           | Consent of independent registered public accounting firm.   |                          |            |                |                   | X              |
| 24.1           | Power of Attorney. Reference is made to the signature page hereto.  |                          |            |                |                   | X              |
| 31.1           |   |                          |            |                |                   | X              |

Certification of the Principal Executive Officer pursuant to  
Rule 13a-14(a) or 15d-14(a) of the Securities Exchange  
Act of 1934.

31.2 Certification of the Principal Financial Officer, pursuant to  
Rule 13a-14(a) or 15d-14(a) of the Securities Exchange  
Act of 1934.

X

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| Exhibit<br>Number | Description of Document  | Incorporate by Reference |          |                |                               |
|-------------------|--|--------------------------|----------|----------------|-------------------------------|
|                   |  | Form                     | File No. | Date of Filing | Exhibit Filed<br>No. Herewith |
| 32.1(1)           | Certification of the Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. |                          |          |                | X                             |
| 32.2(1)           | Certification of the Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. |                          |          |                | X                             |
| 101.INS           | XBRL Instance Document.  |                          |          |                | X                             |
| 101.SCH           | XBRL Taxonomy Extension Schema Document.   |                          |          |                | X                             |
| 101.CAL           | XBRL Taxonomy Extension Calculation Linkbase Document.   |                          |          |                | X                             |
| 101.DEF           | XBRL Taxonomy Extension Definition Linkbase Document.  |                          |          |                | X                             |
| 101.LAB           | XBRL Taxonomy Extension Labels Linkbase Document.  |                          |          |                | X                             |
| 101.PRE           | XBRL Taxonomy Extension Presentation Linkbase Document   |                          |          |                | X                             |

\*Previously filed.

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

‡Indicates management contract or compensatory plan.

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

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