# 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, 2022**

☐ **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 Incorporation or Organization)** | **(I.R.S. Employer Identification No.)** |
| **805 Las Cimas Parkway Suite 100 Austin, TX** | **78746** |
| **(Address of Principal Executive Offices)** | **(Zip Code)** |

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

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

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

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

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

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

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

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

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

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

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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, 2022 (the last business day of the Registrant's second fiscal quarter), based upon the closing price of $0.51 of the Registrant's common stock as reported on The Nasdaq Global Market, was approximately $30.3 million.

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

| Class | Outstanding at February 21, 2023 |
|---|---|
| Common stock, $0.0001 par value per share | 65,395,159 shares |

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the Registrant's Definitive Proxy Statement ("Proxy Statement") relating to the 2023 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the end of the Registrant's 2022 fiscal year and is incorporated by reference into Part III of this Report.

## TABLE OF CONTENTS

## NOTE ABOUT FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and Section 27A of the Securities Act of 1933, as amended, or the Securities Act. All statements contained in this Annual Report other than statements of historical fact, including statements regarding our future results of operations and financial position, business strategy, the length of time that we believe our existing cash resources will fund operations, market size, potential growth opportunities, nonclinical and clinical development activities, efficacy and safety profile of our product candidates, potential therapeutic benefits and economic value of our product candidates, use of net proceeds from our public offerings, our ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of nonclinical studies and clinical trials, commercial collaboration with third parties, and our ability to recognize milestone and royalty payments from commercialization agreements, the expected impact of macroeconomic conditions, including inflation, increasing interest rates and volatile market conditions, as well as global events, including the COVID-19 pandemic and the recent military conflict in Ukraine on our operations, and the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, are forward-looking statements. The words “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “predict,” “target,” “intend,” “could,” “would,” “should,” “project,” “plan,” “expect,” and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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

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

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

## PART I

### ITEM 1. BUSINESS

#### Overview

We are a clinical-stage biotechnology company developing human enzyme therapeutics to benefit people with rare metabolic diseases. Our vision is to redefine what was thought possible and pioneer bold science to deliver groundbreaking medicines to devastating rare diseases. Our two clinical programs are pegtarviliase for Homocystinuria and pegzilarginase for Arginase 1 Deficiency. Both clinical programs are focused on the underlying key metabolites that drive the clinical manifestations of these devastating rare metabolic diseases. We are on a mission to change lives by bringing innovative therapies to underserved rare disease communities.

Pegtarviliase is currently being investigated for the treatment of Classical Homocystinuria. The drug is an investigational PEGylated, or polyethylene glycol modified, human enzyme engineered to reduce elevated levels of total homocysteine, or tHcy, circulating in the plasma. Homocystinuria is a rare genetic disease characterized by elevated plasma homocysteine levels, which can result in debilitating, often irreversible, neurologic, psychiatric, ocular and skeletal complications, and life-threatening vascular events. There are various etiologies leading to Homocystinuria and Classical Homocystinuria is specifically characterized by a deficiency in the cystathionine β-synthase (CBS) enzyme. Currently available treatments for Classical Homocystinuria are burdensome and have limited effectiveness in reducing tHcy for most patients, resulting in a significant unmet need for patients.

Pegzilarginase is a recombinant human arginase 1 that is engineered to enzymatically degrade the amino acid arginine to reduce elevated levels of arginine in patients with Arginase 1 Deficiency. Arginase 1 Deficiency is a rare, inherited metabolic disorder with progressive, debilitating neurologic manifestations driven by persistently high arginine levels. There are currently no approved therapies that address the underlying driver of the disease, and most patients experience long-term clinical deterioration, including neuromuscular and cognitive decline, with current standard of care.

#### Our Strategy

We believe there is significant potential to address rare metabolic diseases through human enzyme therapies and are committed to the development and commercialization of therapeutics that address unmet medical needs for these patient populations. Our strategy is to develop treatments for rare metabolic diseases where we believe there is a causal link between disease development and progression, and levels of key metabolites that drive the clinical manifestations of the diseases. For our two clinical programs, we have engineered and modified enzymes to have specific characteristics needed to address the underlying metabolic drivers of the diseases. For example, pegtarviliase was modified to have specificity for both the monomer and dimer forms of homocysteine and pegzilarginase was modified to have increased arginine-degrading activity. We selected therapeutic candidates for clinical development based on strong biological rationale and robust preclinical evidence to support a potential therapy that can transform patient outcomes.

Our primary focus is the advancement of pegtarviliase through clinical development, regulatory approval and into commercialization. We believe pegtarviliase has the potential to be a best-in-class enzyme therapy for the treatment of Classical Homocystinuria. Pegtarviliase is currently being studied in a Phase 1/2 clinical trial to assess safety and efficacy in patients with Classical Homocystinuria, also known as Homocystinuria due to cystathionine β-synthase deficiency. We estimate that there are approximately 30,000 Classical Homocystinuria patients in global addressable markets, or the 38 countries with a combination of sufficient census data and other commercial elements (e.g., IP protection, access and reimbursement framework), and we estimate about 80% of these patients are unable to control their tHcy levels to targeted clinical thresholds with the currently available treatments. With significantly elevated homocysteine levels, these patients are continuing to experience irreversible progression and remain at risk for catastrophic thromboembolic events resulting in death.

Our other clinical program is pegzilarginase for the treatment of Arginase 1 Deficiency. We reported positive topline data for pegzilarginase for our global pivotal PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial in December 2021 and are continuing to evaluate the safety of pegzilarginase in an open-label study for patients who participated in our previously completed trials. Based on the results from PEACE and a previous Phase 1/2 clinical trial, a Marketing Authorization Application, or MAA, was submitted to the European Medicines Agency, or EMA, by Immedica Pharma AB, or Immedica, our commercial partner in Europe and several countries in the Middle East. We announced in August 2022 that the MAA was validated by the EMA and is currently under review. We submitted a Biologics License Application, or BLA, to the U.S. Food and Drug Administration, or FDA, for pegzilarginase and announced in June 2022 that we had received a Refuse to File, or RTF, letter from the FDA. The FDA requested additional data to support effectiveness, such as evidence showing that plasma arginine and metabolite reduction predicts clinical benefit in patients with ARG1-D or clinical data demonstrating a treatment effect on clinically meaningful outcomes. Previously the agency had

requested an additional randomized placebo-controlled trial of a duration longer than 24 weeks given that efficacy data based on effort-dependent clinical outcome assessments and related endpoints have a high potential for bias. The FDA also requested additional information relating to Chemistry Manufacturing and Controls, or CMC, in the RTF letter. Dialogue with the FDA regarding the pegzilarginase BLA is ongoing.

In addition to our clinical programs, we have leveraged enzyme engineering to create additional pipeline candidates for the treatment of Cystinuria and other undisclosed diseases. These programs represent innovative solutions for diseases that previously were not believed to be addressable with enzyme therapies. For example, Cystinuria is a rare genetic disease characterized by frequent and recurrent kidney stone formation due to increased amounts of cystine in the urine. We engineered and optimized AGLE-325 to reduce plasma cystine and cysteine levels and therefore reduce urine cystine concentrations as an approach to inhibit cystine crystal and kidney stone formation. We announced in January 2023 that we are halting work on our preclinical pipeline candidates, including AGLE-325 for Cystinuria and that we will evaluate potential strategic options for these programs in order to maximize value.

In developing programs for diseases with substantial unmet medical need, we seek opportunities with meaningful commercial potential. We intend to maximize the commercial opportunity and value for each of our product candidates by pursuing regulatory approval in the United States and other select regions on our own or with commercial partners. We retain worldwide intellectual property rights for pegtarviliase and all other preclinical product candidates. We retain all intellectual property rights for pegzilarginase in the United States and other regions outside of our commercial partnership with Immedica in Europe and several countries in the Middle East.

## Our Therapeutic Candidates

### *Pegtarviliase in Homocystinuria*

*Overview:* Pegtarviliase is a novel polyethylene glycol modified, or PEGylated, human enzyme engineered to reduce elevated levels of total homocysteine circulating in the plasma. We engineered pegtarviliase by directed mutagenesis of amino acids within the wild-type human cystathionine γ-lyase enzyme, or CGL. The resultant enzyme has high substrate specificity for both the monomer and dimer forms of homocysteine but not for the native substrate, cystathionine. We believe that by rapidly driving down levels of total homocysteine in the blood, which includes the monomer, dimer and protein-bound forms of homocysteine, it will pull homocysteine out of tissues and cells and into the blood through equilibration. Pegtarviliase in the blood can continue to metabolize total homocysteine to drive lower systemic levels. Classical Homocystinuria patients experience fewer disease complications and improved outcomes with lower total homocysteine levels.

*Selection of Enzyme and Enzyme Characteristics:* In normal homocysteine metabolism, the CBS enzyme acts intracellularly to combine serine with the monomer form of homocysteine to form cystathionine. The presence of serine is required for CBS activity. In Classical Homocystinuria patients, intracellular homocysteine accumulates and eventually leads to increased extracellular levels through equilibration. In the blood, we believe approximately 30% of total homocysteine exists in a dimer or disulfide form, known as homocystine, and approximately 1% in the monomer form. The remaining total homocysteine in the blood is believed to be protein bound.

There are four main mechanistic characteristics that we believe are important for pegtarviliase as a potential therapy for Classical Homocystinuria: the ability to metabolize monomer and dimer forms of homocysteine, lyase versus synthase mechanism, durable pharmacokinetic activity, and potential immunological advantages. CGL is the enzyme that metabolizes cystathionine into cysteine and through targeted mutagenesis of CGL in the development of pegtarviliase we changed the target substrate to homocysteine with the ability to degrade both the monomer and dimer forms. Additionally, pegtarviliase is a lyase enzyme and cleaves homocysteine into other naturally occurring metabolites that are further metabolized and cleared. This means that the serine that is required in the normal intracellular metabolism with CBS is not required when pegtarviliase metabolizes homocysteine in the blood. Pegtarviliase was also PEGylated to increase the stability and half-life in plasma. These pharmacokinetic characteristics could lead to a longer exposure and duration of action as well as potentially increase the time required between doses. We believe these characteristics of pegtarviliase will lead to a faster and more durable reduction of total homocysteine. Lastly, patients with Classical Homocystinuria very likely have normal CGL. Starting with the wild-type CGL enzyme as a scaffold for pegtarviliase may reduce any potential immunogenicity to pegtarviliase.

*Phase 1/2 Open-Label Study of Pegtarviliase in Patients with Classical Homocystinuria*: We are currently conducting a Phase 1/2 clinical trial for the treatment of patients with Classical Homocystinuria to assess the safety and clinical activity of pegtarviliase. The primary objective of the trial is to evaluate the safety and tolerability of pegtarviliase in participants with Classical Homocystinuria. As a secondary objective, the trial will also characterize the pharmacokinetics and pharmacodynamics, as measured as the magnitude of change in plasma tHcy, of pegtarviliase after multiple doses following intravenous and subcutaneous administration. In cohorts 1 through 3, we plan to enroll approximately 12 patients diagnosed

with Classical Homocystinuria, aged 12 years or older (18 or older in the U.S.) with plasma homocysteine levels of 50 µM or greater at screening, and with a history of tHcy greater than or equal to 80 µM. Patients will be dosed once weekly for four weeks, with three to four patients in each of the dosing cohorts.

In March 2022 and August 2022, we announced the completion of the first and second dose cohorts, respectively. The first cohort, 0.15 mg/kg delivered intravenously, included three patients. Pegtarviliase was well tolerated with no safety concerns and data from this cohort showed reductions in tHcy in all three patients. Patients in the second cohort and third cohorts received 0.45 mg/kg and1.35 mg/kg, respectively, via subcutaneous administration. In November 2022, we announced that two patients in the third cohort of the Phase 1/2 clinical trial had completed dosing and that enrollment was ongoing. The decision to enroll patients in cohorts 4 and 5 and the design of these cohorts (e.g., dose level, duration, etc.) will depend on the data gathered from cohorts 1 through 3.

*Regulatory:* We have obtained Orphan Drug Designation from the FDA and EMA for pegtarviliase for the treatment of patients with Homocystinuria. In addition, the FDA granted Fast Track and Rare Pediatric Disease designations for pegtarviliase for the treatment of Homocystinuria. These designations do not necessarily lead to faster development or regulatory review of pegtarviliase, or increase the likelihood that it will receive marketing approval. The Rare Pediatric Disease designation by the FDA provides the potential to receive a Priority Review Voucher if a qualifying BLA for pegtarviliase is approved before October 1, 2026.

In October 2022, we received a letter from the FDA regarding our protocol amendment for the Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria. The protocol amendment, among other things, allowed the inclusion of adolescent patients at clinical trial sites in the United States. The FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less than 18 years of age under this investigational new drug application, or IND, at this time. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. Neither site has pediatric patients currently enrolled and no pediatric patients are pending enrollment at those sites. Both sites can continue to enroll adult patients. We intend to address the feedback from the FDA and aim to satisfy the requirements for prospective benefit for future inclusion of pediatric patients under the IND, including in a potential pivotal trial as well as engaging with the local Australian ethics committee.

We plan to engage with the FDA on next steps for the program, including the design of a potential pivotal trial, when sufficient data from the Phase 1/2 clinical trial are available.

***Homocystinuria overview***

Homocystinuria is an inherited disorder of the methionine metabolism pathway, or transsulfuration pathway, that results in elevated homocysteine and its dimer, homocystine in plasma and urine. This leads to a broad range of serious consequences, such as lens dislocation, skeletal abnormalities, vascular complications and neurologic disorders, as well as the potential for sudden and early death.

There are multiple forms of Homocystinuria that are distinguished by their mutation as well as some manifestations. The most common form of the disease is Classical Homocystinuria, or CBS deficiency. There are over 160 genetic mutations identified that adversely impact CBS enzyme activity to a variable degree impacting the level of tHcy and the response to some treatments. The vast number of mutations that can lead to Classical Homocystinuria result in a clinically heterogenous disorder, with some patients experiencing a more severe form of the disease than others.

The goal of treatment for Classical Homocystinuria is to maintain consistent plasma tHcy levels below the currently defined biochemical targets. Current disease management is lifelong and includes dietary protein (methionine) restriction with amino acid replacement either alone or with vitamin B6 (pyridoxine), and betaine supplementation, which is generally insufficient to effectively control all but the mildest form of the disease. As is the case with other medical diets, adherence is challenging, and nutrient supplementation is often necessary to prevent deficiencies that arise from a lack of normal natural dietary protein intake. Other treatments include high doses of vitamin B6, a cofactor for the CBS enzyme, and betaine, a remethylation agent that converts homocysteine back into methionine. Although betaine is considered to be generally well tolerated, some patients dislike the taste and/or fishy odor and often large doses are required multiple times each day, both of which may lead to poor compliance. Additionally, a risk of hypermethioninemia and cerebral edema has been reported with the use of betaine. While no long-term prospective data exists, recent guidelines based on expert review recommend a target tHcy of less than 100 µM for those that are unresponsive to vitamin B6, although some physicians aim for even lower targets with a combination approach.

Some Classical Homocystinuria patients respond to vitamin B6, resulting in decreases of homocysteine, and are considered B6-responsive. B6-responsive patients have a less severe form of the disease as they are able to keep their homocysteine levels below the clinical guideline of 50 µM with B6 treatment alone. However, many patients are unable to achieve target levels of tHcy through administration of vitamin B6 in addition to the standard of care. These patients are

considered B6-non-responsive or B6-partially-responsive. Because these patients are unable to maintain tHcy levels below the recommended guidelines, they are at higher risk of disease progression and serious complications, including death.

Due to the effect of different mutations leading to various levels of enzyme activity and response to treatment, some subjects have severe childhood-onset multisystem disease, while others may be undiagnosed into adulthood. While newborn screening is universally implemented in the U.S. (and widely available elsewhere), publications have shown that only approximately 50% of cases are detected due to technical limitations of the test. Patients can present with Homocystinuria in childhood with a significant event, such as thrombosis, ocular lens dislocation, severe myopia, skeletal fracture, and/or other manifestations such as developmental delay or cognitive impairment. In adulthood, the most common presentation is with a thrombotic event. Untreated, the disease results in higher mortality, with B6-non-responsive patients having a 23% mortality rate by the age of 30. Publications have shown that outcomes are better in patients with lower tHcy with fewer complications and improved intellectual function.

Based on an internal analysis of published literature and other data sources, we estimate the prevalence of Classical Homocystinuria to be approximately 30,000 in global addressable markets, with approximately 80% of those patients being potential treatment candidates due to their inability to control tHcy levels with currently available treatments. Of the approximately 25,000 treatment candidates in global addressable markets, including B6-non-responsive and B6-partially-responsive patients, approximately 8,500 are estimated in the key commercial markets of the United States, France, Germany, Italy, Spain, and the United Kingdom. We believe the lack of effective interventions to directly address the consequences of Classical Homocystinuria support the need for a therapy to reduce the harmful effects of persistently raised tHcy. Elevated tHcy levels have been linked to severe morbidity and mortality, and therefore the primary goal of any therapy is to reduce homocysteine levels below clinically relevant levels.

***Pegzilarginase in Arginase 1 Deficiency***

*Overview:* Pegzilarginase is a PEGylated, recombinant human arginase 1 that enzymatically degrades the amino acid arginine. We engineered pegzilarginase with modifications that enhance the stability and arginine-degrading activity of the enzyme in human plasma. For Arginase 1 Deficiency, which is a rare progressive disease characterized by high levels of arginine, we believe pegzilarginase may reduce the harmful effects caused by the accumulation of high levels of arginine and other arginine-derived metabolites. Current treatment guidelines focus on the reduction of arginine levels in order to slow disease progression.

*PEACE - Global Pivotal Phase 3 Study of Pegzilarginase in Patients with Arginase 1 Deficiency:* We announced topline results from the double-blind placebo-controlled portion of our PEACE Phase 3 trial in December 2021. The trial is believed to be the first-ever investigative therapy that directly addresses the high arginine levels that are believed to be the key drivers of this devastating disease for patients with Arginase 1 Deficiency.

PEACE was a global, randomized, double-blind, placebo-controlled trial designed to assess the effects of treatment with pegzilarginase versus placebo over 24 weeks with a primary endpoint of statistically significant plasma arginine reduction from baseline. The primary endpoint assessed the effectiveness of pegzilarginase in lowering plasma arginine levels. Secondary endpoints included clinical outcome assessments focused primarily on measuring the impact on functional mobility, including the key secondary endpoints consisting of Gross Motor Function Measure Part E, or GMFM-E, and 2 Minute Walk Test, or 2MWT, in addition to safety and pharmacokinetics.

The pivotal trial enrolled 32 patients aged two years and older, who had plasma arginine levels greater than 250 μM and a baseline deficit in at least one clinical response assessment. Patients enrolled in the trial were randomized on a two-to-one basis to receive weekly infusions of pegzilarginase (0.1 mg/kg starting dose), or placebo for the double-blind treatment period. Dose adjustments during this period were allowed in order to optimize plasma arginine control. Patients remained on current disease management for the duration of the PEACE Phase 3 trial. Upon completion of the 24-week treatment period, patients were eligible to participate in a long-term extension study of pegzilarginase, with all 31 patients who completed the double-blind period continuing into the long-term extension study and switching to subcutaneous administration.

In December 2021, we announced the topline results for the PEACE Phase 3 trial. In April 2022 and August 2022, we presented data from our ongoing PEACE Phase 3 trial at the Society for Inherited Metabolic Disorders, or SIMD, and at the Society for the Study of Inborn Errors of Metabolism, or SSIEM, respectively. Highlights from the PEACE Phase 3 trial to date are summarized as follows:

- Primary endpoint was achieved with a highly statistically significant 76.7% reduction in mean plasma arginine in pegzilarginase treated patients ($p<0.0001$) compared to the placebo arm.
- Normal plasma arginine levels (40-115 μM) were achieved in 90.5% of pegzilarginase treated patients compared to no patients in the placebo arm.

- Accompanying improvements in the key secondary mobility assessment endpoint in pegzilarginase treated patients compared to the placebo arm.
    - Gross Motor Function Measure Part E (GMFM-E): The least squares mean score improved by 4.2 units for pegzilarginase treated patients and worsened by 0.4 units in the placebo arm (p=0.1087), establishing a positive trend.
    - 2-minute walk test (2MWT): The least squares mean distance increased 7.4 meters in pegzilarginase treated patients and 1.9 meters in the placebo arm (p=0.5961).
- Pegzilarginase was well-tolerated, and safety data were consistent with results from previous clinical trials. Serious adverse events included hyperammonemia and vomiting, which were infrequent, expected, and managed with standard treatment. There were no study discontinuations due to treatment-emergent adverse events.
- In an analysis of individual patients that were Gross Motor Function Classification System (GMFCS) Level I-III with predefined clinical response criteria there were clinically important differences between the pegzilarginase treated patients (n=17) and the placebo arm (n=9).
    - Eleven pegzilarginase treated patients (65%) reached or exceeded prespecified response criteria for at least one mobility assessment compared to four patients (44%) in the placebo arm.
    - Eight pegzilarginase treated patients (47%) met or exceeded prespecified clinical response criteria for at least two of the mobility outcomes compared to no patients in the placebo arm.

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

*Phase 2 Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability and Effects of Pegzilarginase in Patients with Arginase 1 Deficiency Who Received Treatment in a Previous Study:* After completing the repeat dose portion of the Phase 1/2 study and at least three weeks of post-treatment observation, patients were allowed to continue treatment with pegzilarginase, including subcutaneous administration, by enrolling in a long-term open-label extension study. All 14 eligible patients enrolled in the Phase 2 open-label extension trial and all ongoing patients switched to subcutaneously dosed pegzilarginase when permitted.

We announced 20-week and 56-week data on 14 and 13 patients, respectively, from our completed Phase 1/2 trial and ongoing Phase 2 open-label extension trial for pegzilarginase in patients with Arginase 1 Deficiency. In each of the interim data announcements, we reported all patients continued to demonstrate marked and sustained reductions in plasma arginine following 20-weeks and 56-weeks of pegzilarginase administration and 79% (11 of 14) and 85% (11 of 13) of patients were clinical responders, respectively, based on a clinically meaningful improvement in one or more of three complementary mobility assessments. For GMFM-E, the mean change from baseline at the 56-week analyses was 6 units. When analyzing the subset of patients who had a baseline deficit (seven patients), the mean change for GMFM-E was 9 units. For the 6 Minute Walk Test, or 6MWT, the mean change from baseline at the 56-week analyses was 45 meters. Pegzilarginase was well tolerated and the rates of treatment-related adverse events decreased over time. Serious adverse events included hypersensitivity and hyperammonemia, which were infrequent, expected, and managed with standard treatment and did not lead to any patient discontinuations.

Additionally, we announced 104-week mobility data from our completed Phase 1/2 trial and ongoing Phase 2 open-label extension trial on the nine patients that had completed assessments through the period. The mean change from baseline for GMFM-E and the 6MWT was 7 units and 38 meters, respectively, at the 104-week analyses. The clinical outcome assessment represented continued improvements over baseline after two years on treatment with pegzilarginase in the context of a progressive disease.

*Regulatory:* In August 2022, we announced that the EMA had validated the MAA, for pegzilarginase for the treatment of Arginase 1 Deficiency that was submitted by Immedica our commercialization partner in Europe and several countries in

the Middle East. Review of the MAA is underway, and a decision from the EMA with respect to approval of pegzilarginase may occur in late 2023.

In April 2022, we announced that after careful consideration and further review of the efficacy and safety data from the ongoing PEACE Phase 3 trial, including the updated efficacy data from that trial and long-term safety data from the pegzilarginase program, we submitted a BLA to the FDA in order to provide all the study results for the FDA to review in detail.

In June 2022, we announced that we received a RTF letter from the FDA for the BLA for pegzilarginase for the treatment of Arginase 1 Deficiency. In the RTF letter, the FDA requested additional data to support effectiveness, such as evidence showing that plasma arginine and metabolite reduction predicts clinical benefit in patients with ARG1-D or clinical data demonstrating a treatment effect on clinically meaningful outcomes. The FDA also requested additional information relating to Chemistry Manufacturing and Controls, or CMC. There were no issues related to safety raised in the letter. Upon receipt of the RTF letter, we had 30 days in which to request a Type A meeting with the FDA to clarify and respond to items identified in the RTF letter. The Type A meeting with the FDA was held in July 2022. We continue to engage in dialogue with the FDA to identify a viable regulatory approach and path to BLA resubmission.

We have obtained Orphan Drug designation from the FDA and the EMA, as well as Fast Track and Breakthrough Therapy designations from the FDA, for pegzilarginase for the treatment of patients with Arginase 1 Deficiency. In addition, the FDA granted a Rare Pediatric Disease designation for pegzilarginase for the treatment of Arginase 1 Deficiency. These designations do not necessarily lead to faster development or regulatory review of pegzilarginase, or increase the likelihood that it will receive marketing approval. The Rare Pediatric Disease designation by the FDA confirms our eligibility to receive a Rare Pediatric Disease priority review voucher if a qualifying BLA for pegzilarginase is approved before October 1, 2026.

*Licensing:* We licensed to Immedica the rights to the commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman. The license and supply agreement, or Immedica Agreement, we entered into with Immedica includes a non-refundable upfront payment of $21.5 million from Immedica and development services provided to Immedica, up to $3.0 million. Under the terms of the Immedica Agreement, we are eligible to receive additional payments of up to approximately $120.8 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.07 to €1.00. Additionally, we are entitled to receive royalties in the mid-20 percent range on net sales of the product in countries included in the Immedica Agreement. We will continue to be responsible for certain clinical development activities and the manufacturing of pegzilarginase and we retain commercialization rights in the United States and the rest of the world.

***Arginase 1 Deficiency overview***

Arginase 1 Deficiency is a rare, inherited metabolic disorder with progressive, debilitating neurologic manifestations driven by persistent high arginine levels resulting from impaired arginase 1 activity. This leads to two important harmful metabolic effects: (1) the accumulation of high levels of arginine and other arginine derived metabolites, and (2) an impairment of the urea cycle which potentially leads to intermittent elevation of ammonia levels, especially at times of stress. The high plasma arginine level is believed to be the key driver of the spasticity, developmental delays, and seizures that develop in early childhood and progress over time. The impairment of the urea cycle also means that these patients are at risk of episodic and sometimes persistent hyperammonemia, which causes irritability, nausea, and vomiting with potential to progress to brain swelling, encephalopathy, reduced life expectancy, and death.

The current standard of care is inadequate to sufficiently lower arginine levels, and most patients experience continued progression, increasing morbidity, and early mortality. Current disease management practice includes a medical diet with protein restriction, ammonia scavengers, and adjustments to essential amino acids. Medical literature suggests that disease progression can be slowed with strict adherence to dietary protein restriction, which often includes the use of specially formulated supplements. Such dietary modification has been shown to partially reduce plasma arginine levels, but generally does not consistently reach the range stipulated by medical guidelines. Therefore, this disease management approach is generally inadequate to treat the majority of patients, unpalatable, and difficult to manage. Ammonia-scavenging drugs such as RAVICTI® (glycerol phenylbutyrate) and BUPHENYL® (sodium phenylbutyrate) are used to manage elevated ammonia levels. In some cases, liver transplantation has been utilized to treat Arginase 1 Deficiency; however, this intervention is available only to a small fraction of patients and carries significant procedural risk. There is a significant unmet need for treatment that effectively lowers arginine levels and prevents clinical deterioration in the long term.

The lack of effective treatment options that directly address the cause of Arginase 1 Deficiency supports the need for a therapy that manages the harmful metabolic effects caused by accumulation of high levels of arginine and other arginine-derived metabolites (also referred to as guanidino compounds). We believe introducing an arginine-reducing therapeutic early in a patient's life could potentially minimize the exposure to the neurotoxic effects of elevated arginine and its metabolites, as well as potentially enable increased protein intake. We believe that reduction and maintenance of plasma

arginine levels to within levels recommended by medical guidance for an extended period during the pegzilarginase dosing schedule has the potential to slow or halt the progression of the disease, thereby offering the potential for more normal growth and development in these patients.

Arginase 1 Deficiency is a rare disorder, and disease prevalence has not been well established in the medical literature. Based on a published genetic prevalence analysis, we estimate that the Arginase 1 Deficiency population is greater than 2,500 patients in the global addressable markets and greater than 1,150 patients in the territories with regulatory and launch plans underway. The genetic prevalence-based methodology has the ability to account for misdiagnosis of the disease and to address limitations in newborn screening methodology, including naturally low arginine levels in newborns and lack of geographic availability or standardization of testing. Presently, only 34 U.S. states screen for Arginase 1 Deficiency, and screening in Europe is not universal. Because the manifestations of Arginase 1 Deficiency may overlap with other disorders such as hereditary spastic paraplegia, cerebral palsy or epilepsy, the prevalence of Arginase 1 Deficiency may be underestimated. We continue to make progress in patient identification, and insights from these efforts serve as a foundation for our potential commercialization strategy and execution.

### *AGLE-325 in Cystinuria and other research programs*

Cystinuria is a rare genetic disease characterized by frequent and recurrent kidney stone formation requiring multiple procedural interventions, and by an increased risk of chronic kidney disease. Cystinuria occurs due to genetic mutations in amino acid transporters that lead to increased amounts of cystine in the urine. This results in high cystine concentrations in the urine and formation of kidney stones. As such, we engineered and optimized AGLE-325 to reduce plasma cystine and cysteine levels with accompanying reductions in urine cystine concentrations as an approach to inhibit both cystine crystal and kidney stone formation. We presented preclinical data on a precursor molecule to AGLE-325 demonstrating reduced kidney stone formation in a preclinical model of Cystinuria.

In January 2023, we announced work on our preclinical pipeline candidates, including AGLE-325 for Cystinuria, would be halted and potential strategic options for these programs would be evaluated in order to maximize the value of those programs.

## Intellectual Property

Our policy is to seek to protect our proprietary position by filing U.S. and foreign patent applications related to our proprietary technology, including both new inventions and improvements of existing technology, that are important to the development of our business, unless this proprietary position would be better protected using trade secrets. Our patent strategy includes obtaining patent protection, where possible, on compositions of matter, methods of manufacture, methods of use, combination therapies, dosing and administration regimens, formulations, therapeutic monitoring, screening methods, and assays. We also rely on trade secrets, know-how, continuing technological innovation, in-licensing, and partnership opportunities to develop and maintain our proprietary position. Lastly, we monitor third parties for activities that may infringe our proprietary rights, as well as the progression of third-party patent applications that may have the potential to create blocks to our products or otherwise interfere with the development of our business.

### *Patents*

We are the exclusive licensee of granted U.S. and Japanese patents and pending foreign counterpart patent applications directed towards the pegtarviliase program. The patents and patent applications cover recombinant human enzymes that degrade the amino acids homocysteine and homocystine. Any patents that issue from these applications will expire in 2038 absent any patent term adjustment or patent term extension. We also own U.S. and foreign counterpart patent applications directed towards methods of treatment of homocystinuria. Any patents that issue from these patent applications will expire in 2040, absent any patent term adjustment or patent term extension.

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

pegzilarginase, and any patents that issue from these applications will expire in 2040, absent any patent term adjustment or patent term extension.

We also are the exclusive licensee of U.S. and European patents and applications, as well as foreign counterpart patents and applications, directed towards modified CGL enzymes with activity to degrade plasma cystine and cysteine and the use thereof. These patents and any further patents issued from these patent applications will expire between 2034 and 2039, absent any patent term adjustment or patent term extension.

We are also the exclusive licensee of U.S., European, Chinese, and Japanese patents and foreign counterpart patents and patent applications directed towards modified CGL enzymes with activity to degrade the amino acid methionine. These patents and any further patents that issue from these patent applications will expire in 2034, absent any patent term adjustment or patent term extension. We own U.S. and European patents and foreign counterpart patents and patent applications directed towards compositions of methioninases. These patents and any further patents that issue from these patent applications will expire in 2031, absent any patent term adjustment or patent term extension.

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 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**

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, or the University, for certain intellectual property owned by the University related to cystinase and methioninase. In January 2017, we and the University entered into an Amended and Restated Patent License Agreement, or the Restated License, which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to the Company. The Restated License was amended in August 2017, December 2017, and December 2018 to revise diligence milestones and license additional patent applications, including the Company's program candidates under the pegtarviliase and Cystinuria programs.

With respect to each program candidate covered by the Restated License, we could be required to pay the University up to $6.4 million in milestone payments based on the achievement of certain development milestones, including clinical trials and regulatory approvals, the majority of which are due upon the achievement of later development milestones, including a $5.0 million payment due on regulatory approval of a product and a $0.5 million payment payable on final regulatory approval of a product for a second indication. In addition, we are required to pay the University a low single digit royalty on worldwide-net sales of products covered under the Restated License, together with a revenue share on non-royalty consideration received from sublicensees. The rate of the revenue share ranges from 6.5% to 25%, depending on the date the sublicense agreement is signed. The term of the Restated License continues until the expiration of the last to expire of the patents licensed thereunder. The University may terminate the agreement under certain circumstances, including for a breach by us that is not cured within 30 or 60 days of notice (depending on the type of breach), or if we or any of our affiliates or sublicensees participate in any proceeding to challenge the licensed patent rights (unless, with respect to sublicensees, we terminate the applicable sublicense). As of December 31, 2022, we have paid $0.4 million under these license agreements.

In March 2021, we entered into the Immedica Agreement, pursuant to which Immedica licensed the product rights for commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman. In April 2021, we received an upfront payment of $21.5 million from Immedica. Under the terms of the Immedica Agreement, we are also eligible to receive additional payments of up to approximately $120.8 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.07 to €1.00. Additionally, we are entitled to receive royalties in the mid-20 percent range on the net sales of the product in countries included in the Immedica Agreement.

***Grant Agreement***

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

Pursuant to the Grant Contract, we granted to CPRIT a non-exclusive, irrevocable, royalty-free, perpetual, worldwide license to any technology and intellectual property resulting from the grant-funded activities and any other intellectual property that is owned by us and necessary for the exploitation of the technology and intellectual property resulting from the grant-funded activities, or the Project Results, for and on behalf of CPRIT and other governmental entities and agencies of the State of Texas and private or independent institutions of higher education located in Texas for education, research and other non-commercial purposes only. The terms of the Grant Contract require that we pay tiered royalties in the low- to mid-single digit percentages on revenues from sales and licenses of products or services that are based upon, utilize, are developed from or materially incorporate Project Results. Such royalties are reduced to less than one percent after a mid-single-digit multiple of the grant funds have been repaid to CPRIT in royalties. Such royalties are payable for so long as we have marketing exclusivity or patents covering the applicable product or service (or 12 years from first commercial sale of such product or service in certain countries if there is no such exclusivity or patent protection).

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

**Competition**

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

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

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

With respect to pegtarviliase for Homocystinuria, there is currently one FDA-approved prescription therapy for the treatment of Homocystinuria and several medical foods for the dietary management of individuals with Homocystinuria. The primary treatment goal in patients with Homocystinuria is to maintain consistent plasma tHcy levels below the currently defined biochemical targets. Current disease management practice for the majority of Homocystinuria patients consists of dietary restriction, vitamin B6, vitamin B12, folate supplementation, medical foods, and betaine. CYSTADANE® (betaine anhydrous for oral solution) was approved by the FDA in 1996 for the treatment of Homocystinuria, and Recordati Rare Diseases Inc. currently owns the North American marketing rights to this product. Medical foods are manufactured by Breckenridge Pharmaceutical, Inc. and Upsher-Smith Laboratories, LLC.

We are also aware of a limited number of investigational therapies for the treatment of Homocystinuria. Travere Therapeutics Inc. is focused on the development of pegtibatinase, an enzyme replacement therapy in patients with Homocystinuria due to cystathionine β-synthase deficiency. Travere released topline data in December 2021 from its Phase 1/2 study of pegtibatinase which showed a 55% reduction in homocysteine at the highest dose cohort (1.5mg/kg, 2x/week). In January 2023, Travere stated that enrollment had been completed in the final cohort of their ongoing Phase 1/2 study and that the company is preparing for the initiation of a pivotal Phase 3 trial in the second half of 2023. SYNB1353 from Synlogic Inc. is also in clinical development for the potential treatment of Homocystinuria. In January 2023, the company announced completion of a Phase 1 study with anticipated advancement into Phase 2 in 2023. This investigational agent is an oral synthetic biotic platform that consumes methionine, an essential amino acid and precursor of homocysteine, in the gastrointestinal tract. We are also aware of two investigational therapies in preclinical development. The first is CDX-6512, an oral methionine-gamma-lyase enzyme therapy from Codexis. Additionally, Erytech Pharma SA also has a product candidate for Homocystinuria in preclinical development. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Homocystinuria.

With respect to pegzilarginase for Arginase 1 Deficiency, there are currently no effective treatment options or approved therapeutic agents that address the underlying cause of the disease and we are not aware of any other therapeutics that do so in clinical development. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Arginase 1 Deficiency. The current disease management practice for patients with Arginase 1 Deficiency includes one or more of the following: dietary protein restriction, essential amino acid supplementation, and ammonia scavengers. The dietary restrictions with amino acid supplementation are intended to reduce plasma arginine levels, while ammonia scavengers (such as Horizon Therapeutics' RAVICTI® (glycerol phenylbutyrate), BUPHENYL® (sodium phenylbutyrate) and Acer Therapeutics' OLPRUVA™) are used to manage elevated ammonia levels in patients with urea cycle disorders. A small number of companies have an interest in the role of arginine depletion in other therapeutic areas, but we are not aware of any active preclinical or clinical development activities in Arginase 1 Deficiency. In the oncology field, Polaris Group has conducted numerous clinical trials of ADI-PEG 20, an enzyme derived from mycoplasma, and Athenex has conducted preclinical research with PT01, a PEGylated genetically modified human arginase enzyme, in numerous tumor models.

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 diagnostics, in guiding the use of related therapeutics, the level of biosimilar competition and the availability of reimbursement from government and other third-party payors.

**Manufacturing**

We currently contract with third parties for the process development, manufacturing, and testing of our product candidates for nonclinical and clinical studies and intend to do so for future studies as well. We may qualify additional manufacturers to provide potential alternative sources for the drug substance and fill-and-finish services for pegtarviliase and pegzilarginase as the compounds progress through clinical development. We believe we have sufficient supplies of pegtarviliase for our ongoing Phase 1/2 clinical trial for the treatment of patients with Classical Homocystinuria and of pegzilarginase for our open-label extension study for the treatment of patients with Arginase 1 Deficiency who have participated in one of our previous clinical trials.

***The Diosynth Agreement***

In November 2018, we entered into a master services agreement, or the Diosynth Agreement, with Fujifilm Diosynth Biotechnologies UK Limited, Fujifilm Diosynth Biotechnologies Texas, LLC, and Fujifilm Diosynth Biotechnologies U.S.A., Inc., collectively, Fujifilm. Under the Diosynth Agreement, Fujifilm provides research, development, testing and manufacturing services of certain of our products, which are or will be designated as programs pursuant to scope of work agreements. The fees for such services are or will be set out in each scope of work agreement. We may pay additional fees in consideration of certain research and development and technical consultancy services in relation to the procurement,

testing and management of consumables, subcontracted work (including delivery of material to and from such subcontractors), process-specific equipment (including installation and qualification thereof), modifications and special waste. Either party may terminate the Diosynth Agreement by giving six months written notice to the other party, provided there are no uncompleted programs existing at the date such notice is given, or upon material breach. We may also be required to pay Fujifilm cancellation fees in the event that we decide to terminate any scope of work prior to its completion, calculated as a percentage of the fees payable under the applicable scope of work agreement. Additionally, upon providing written notice, we may cancel certain stages or programs for convenience, and Fujifilm may terminate for certain unforeseen technical errors.

**Government Regulation and Product Approval**

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

***FDA approval process***

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

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

Preclinical tests include laboratory evaluation of product chemistry, formulation, and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of some preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. Unless the FDA places the trial in the IND on clinical hold within this 30-day period, the clinical trial proposed in the IND may begin. A clinical hold is an order issued by FDA to the sponsor of an IND application to delay a proposed clinical trial or to suspend an ongoing trial pending the resolution of a potential deficiency in the IND. All or some of the investigations conducted under an IND may be placed on clinical hold. 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 may be sufficient in rare instances where: (1) 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 or (2) the trial has a statistically significant finding in combination with other confirmatory evidence.

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

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

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

After the FDA evaluates the BLA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the BLA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. An approval letter authorizes commercial marketing of the biologic with specific prescribing information for specific indications. As a condition of BLA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the biologic outweigh the potential risks. REMS can include medication guides, communication plans for

healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the product. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the product's safety or efficacy.

Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new BLA or BLA supplement before the change can be implemented. A BLA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing BLA supplements as it does in reviewing BLAs.

***Fast Track designation and accelerated approval***

The FDA is required to facilitate the development, and expedite the review, of drugs or 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 product 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 product candidate qualifies for Fast Track designation within 60 days of receipt of the sponsor's request. In addition to other benefits such as the ability to 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.

Under the FDA's accelerated approval regulations, 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. 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 product candidates approved under accelerated regulations are subject to prior review by the FDA. The FDA may also grant a full approval to a drug or biologic based on a surrogate endpoint when the surrogate biomarker is validated, allowing it to be used in place of a clinical outcome. Validated surrogate endpoints must undergo extensive testing in clinical trials to show they can be relied upon to predict clinical benefit, which is more rigorous than the testing needed to demonstrate that a surrogate endpoint is reasonably likely to predict clinical benefit to support an accelerated approval.

***Breakthrough Therapy designation***

The FDA is also required to expedite the development and review of the application for approval of drug or 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 product 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 product qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request. Additionally, the Breakthrough Therapy 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, including considering any new drug or biologic approvals that later the unmet medical need.

***Orphan Drug designation***

Under the Orphan Drug Act, the FDA may grant Orphan Drug designation to drug or biological products intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a product available in the United States for such disease or condition will be recovered from sales of the product.

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

***Rare Pediatric Disease Priority Review Voucher program***

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

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

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

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

The Rare Pediatric Disease Priority Review Voucher program was reauthorized in the Creating Hope Reauthorization Act in December 2020, allowing a product that is designated as a product for a rare pediatric disease prior to October 1, 2024 to be eligible to receive a Priority Review Voucher upon approval of a qualifying NDA or BLA prior to October 1, 2026.

***Disclosure of clinical trial information***

Sponsors of clinical trials of FDA-regulated products, including biological products, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain

circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

***Pediatric information***

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

***Additional controls for biologics***

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

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

***Patent term restoration***

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

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

***Biosimilars***

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, creates an abbreviated approval pathway for biological products shown to be highly similar to or interchangeable with an FDA-licensed reference biological product. Biosimilarity sufficient to reference a prior FDA-approved product requires that there be no differences in conditions of use, route of administration, dosage form, and strength, and no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency. Biosimilarity must be shown through analytical trials, animal trials, and a clinical trial or trials, unless the Secretary of the U.S. Department of Health and Human Services, or HHS, waives a required element. A biosimilar product may be deemed interchangeable with a prior approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of

the reference biologic. The FDA has approved numerous biosimilar products, and in 2021 approved the first interchangeable product 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) 18 months after resolution of a lawsuit over the patents of the reference biologic in favor of the first interchangeable biosimilar applicant, or (iv) 42 months after the first interchangeable biosimilar's application has been approved if a patent lawsuit is ongoing within the 42-month period.

***Post-approval requirements***

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

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

***FDA regulation of companion diagnostics***

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

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

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application

is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, additional testing and/or restrictions on labeling, promotion, sale and distribution.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also register their establishment(s), including payment of an annual establishment registration fee, and list their device(s) with the FDA. A medical device manufacturer's manufacturing processes, and the processes of the device specification developer and repackager/relabeler (if different from the manufacturer) and initial importer (if manufactured outside of the United States), 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. Facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA.

***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 HHS (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, physician assistants, certain advanced care nurses and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. The reported data are posted in searchable form on a public website on an annual basis. Failure to submit required information may result in civil monetary penalties.

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***

Healthcare reforms that have been adopted, and that may be adopted in the future, could result in further reductions in coverage and levels of reimbursement for pharmaceutical products, increases in rebates payable under U.S. government rebate programs and additional downward pressure on pharmaceutical product prices. On September 9, 2021, the Biden administration published a wide-ranging list of policy proposals, most of which would need to be carried out by Congress, to reduce drug prices and drug payment. This recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which will, among other things, allow the Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D, although only high-expenditure single-source drugs that have been approved for at least 7 years (11 years for biologics) can be selected by CMS for negotiation, with the negotiated price taking effect two years after the selection year. The negotiated prices, which will first become effective in 2026, will be capped at a statutory ceiling price. Beginning in October 2023, the IRA will penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in Affordable Care Act marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. The full economic impact of the IRA is unknown at this time. It is unclear to what extent additional statutory, regulatory, and administrative initiatives will be enacted and implemented.

***The Foreign Corrupt Practices Act***

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

***Additional regulation***

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

***International government regulation***

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

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

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

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

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

**Corporate Information**

We were formed as a limited liability company under the laws of the State of Delaware in December 2013 and converted to a Delaware corporation in March 2015. Our principal executive offices are located at 805 Las Cimas Parkway, Suite 100, Austin, Texas 78746, and our telephone number is (512) 942-2935. Our website address is www.aeglea.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.

**Human Capital Resources**

As of December 31, 2022, we employed 69 people: 66 employees in the United States and 3 employees in international locations. We also engage temporary employees and consultants to augment our existing workforce. None of our employees are represented by a labor union, we have not experienced any work stoppages, and we consider our relations with our employees to be good.

We are committed to providing our employees with a work environment that is free of unlawful discrimination, including any harassment on the basis of any legally protected status. Accordingly, we do not and will not tolerate any form of unlawful harassment against our employees, whether by executives, managers, co-workers, or by third parties, such as vendors, or other third parties with whom our employees interact. In addition, we provide equal employment opportunity to all employees

and applicants for employment and do not discriminate on any basis prohibited by law, including race, color, sex, gender, sexual orientation, pregnancy, age, religion, national origin, disability, marital status, and veteran status.

We recognize that attracting, motivating, and retaining talent at all levels is vital to continuing our success. We invest in our employees through high-quality benefits and various health and wellness initiatives and offer competitive compensation packages (base salary and incentive plans), ensuring fairness in internal compensation practices. The principal purposes of our incentive plans (bonus and equity) are to align with the long-term interests of our stakeholders and stockholders.

To further engage and incentivize our workforce, we offer a wide range of opportunities to support professional development and growth. For our talent pipeline assessment and development, we work closely with individual business functional leaders to identify our high-performing and high-potential employees, by conducting a company-wide talent assessment utilizing a Performance/Potential Matrix assessment tool. This assessment is completed annually to ensure we tie together our incentives, development, and recognition to retain and attract the people we need to drive our success.

**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* and on our website under the "Investors" tab as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

## ITEM 1A. RISK FACTORS

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

### Summary Risk Factors

Our business is subject to a number of risks and uncertainties, including those highlighted in the section titled "Risk Factors" immediately following this summary. Some of these risks are:

- *We and our independent auditors have expressed substantial doubt about our ability to continue as a going concern.*
- *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 depend heavily on the success of our most advanced product candidates, pegtarviliase and pegzilarginase. Existing and future clinical trials of our product candidates, including pegtarviliase and pegzilarginase may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.*
- *The results from our global pivotal PEACE Phase 3 trial may not support marketing approval, and the FDA or other regulatory authorities may require us to conduct additional clinical trials or evaluate current subjects for an additional follow-up period.*
- *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.*
- *Our engineered human enzyme product candidates represent a novel therapeutic approach, which could result in heightened regulatory scrutiny, delays in clinical development, or delays in our ability to achieve regulatory approval or commercialization of our product candidates.*
- *We have only initiated clinical trials for pegtarviliase and pegzilarginase for the treatment of certain conditions. We have not dosed any of our other product candidates in humans. Our existing and future planned clinical trials may reveal significant adverse events, toxicities or other side effects not seen in our nonclinical studies or early stage clinical trials and may result in a safety profile that could inhibit regulatory approval or market acceptance of any of our product candidates.*
- *Delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials could delay or prevent our receipt of necessary regulatory approvals.*
- *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.*
- *If there are delays in obtaining, or we are not able to obtain, 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.*
- *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.*
- *The outbreak of the novel strain of coronavirus, SARS-CoV-2 and its emerging variants, which causes COVID-19, has, and may continue to, adversely impact our business, including supply chain interruptions.*

**Risks Related to Our Financial Position and Need for Additional Capital**

***We and our independent auditors have expressed substantial doubt about our ability to continue as a going concern.***

The Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date the financial statements included in this Annual Report on Form 10-K are issued. Based upon the Company's current operating plans, the Company believes that it has sufficient resources to fund operations into the fourth quarter of 2023 with its existing cash, cash equivalents, and marketable securities. Accordingly, based on its recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance its future operations, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within twelve months of the issuance date of these financial statements.

In view of these matters, our ability to continue as a going concern is dependent upon our ability to raise additional capital through outside sources. We intend to obtain funding through the sale of common stock in public offerings and/or private placements, debt financings, or through other capital sources, including collaborations with other companies or other strategic transactions. The failure to obtain sufficient financing or strategic partnerships could adversely affect our ability to achieve our business objectives and continue as a going concern.

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

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

Other than the PEACE Phase 3 trial of pegzilarginase, we have not demonstrated our ability to successfully complete a pivotal clinical trial. We have not yet demonstrated our ability to successfully obtain marketing approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, other than for pegtarviliase and pegzilarginase, or conduct sales and marketing activities necessary for successful product commercialization. Products, on average, take 10 to 15 years to be developed from the time they are discovered to the time they are approved and available for treating patients. Although we have recruited a team that has experience with clinical trials, as a company we have limited experience in conducting clinical trials. Due to this limited experience, we cannot be certain that planned or ongoing clinical trials will begin or be completed on time, if at all, and/or will yield clinical results that we may expect. 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 conducting clinical trials or commercializing products.

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

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

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

In addition, since inception, we have incurred significant operating losses. For the years ended December 31, 2022 and 2021, we reported a net loss of $83.8 million and $65.8 million, respectively. As of December 31, 2022, we had an accumulated deficit of $425.6 million. Based upon our current operating plans, we believe that we have sufficient resources to fund operations into the fourth quarter of 2023 with our existing cash, cash equivalents, and marketable securities. Accordingly, based on recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our future operations, we determined that there is substantial

doubt about our ability to continue as a going concern within twelve months of the issuance date of the financial statements included in this Annual Report on Form 10-K. We plan to address this condition through the sale of common stock in public offerings and/or private placements, debt financings, or through other capital sources, including collaborations with other companies or other strategic transactions. In the past, we have financed our operations primarily through private placements of our preferred stock, the initial public offering of our common stock, follow-on public offerings of our common stock and pre-funded warrants, collection of a research grant, and the licensing of our product rights for commercialization of pegzilarginase in Europe and several countries in the Middle East. We have devoted substantially all of our efforts to research and development. Currently, we are conducting clinical development for pegtarviliase for the treatment of Homocystinuria and pegzilarginase for the treatment of Arginase 1 Deficiency. We have not initiated clinical development of our other product candidates and none of our product candidates are ready for commercialization. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, and the net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

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

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

To become and remain profitable, we must develop and eventually commercialize a product candidate or product candidates with significant market potential. This will require us to be successful in a range of challenging activities, including completing nonclinical testing, initiating and completing clinical trials of one or more of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those product candidates for which we obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. We reported in April 2022 that we submitted a BLA to the FDA for pegzilarginase for the treatment of Arginase 1 Deficiency and announced in June 2022 that we received a Refuse to File letter, or RTF Letter, from the FDA regarding our BLA submission. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. We are continuing to engage with FDA to identify a potential path to BLA resubmission. In October 2022, we received a letter from the FDA regarding a protocol amendment for our Phase 1/2 clinical trial of pegtarviliase for the treatment of Classical Homocystinuria in which the FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less than 18 years of age. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. We are in the nonclinical development stages for our remaining product candidates. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain or expand our research and development efforts, expand our business or continue our operations.

***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 initiate and continue clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding to support our continuing operations. If we are unable to raise capital when needed for any reason, including but not limited to inflation, increasing interest rates, volatile market conditions and global events, or on acceptable terms, we would be forced to delay, reduce or eliminate our discovery and nonclinical development programs, our ongoing clinical development, or any future clinical development or commercialization efforts.

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 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 commercialization activities, 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.

Even if successful in raising new capital, we could be limited in the amount of capital we raise due to investor demand restrictions placed on the amount of capital we raise or other reasons. For example, as of the filing of this Annual Report, we are subject to the limitations set forth in Instruction I.B.6 of Form S-3 (the "baby shelf restrictions") or other reasons. If we are unable to raise sufficient amounts of capital it could similarly affect our progress and we could be forced to delay, reduce, or eliminate our discovery and nonclinical development programs, our ongoing clinical development, or any future clinical development or commercialization efforts.

Our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products, none of which have been approved to date. 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, collaborations, and license and development agreements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, or if existing holders of warrants exercise their rights to purchase common stock, your ownership interest will be diluted, and the terms of these securities may rank senior to our common stock and include liquidation or other preferences, covenants or other terms that adversely affect your rights as a common stockholder. Further, any future sales of our common stock by us or resale of our common stock by our existing stockholders could cause the market price of our common stock to decline. A decline in the value of our company would also cause you to lose part or even all of your investment. 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.

**Risks Related to Our Product Development and Regulatory Approval**

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

In order to execute on our strategy of advancing the clinical development of our product candidates, we completed the global pivotal PEACE Phase 3 clinical trial and a Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency. We are conducting an open-label study of pegzilarginase for the treatment of Arginase 1 Deficiency, for patients that participated in our previous clinical trials, and a Phase 1/2 clinical trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. If our product candidates fail to work as we expect, or if we need to conduct additional studies to better understand the relationship between our product candidates and clinical activity, (i.e. efficacy and safety), our ability to assess the therapeutic effect, seek regulatory approval or otherwise begin or further clinical development, could be compromised. We announced on August 18, 2022 that a MAA for pegzilarginase for the treatment of Arginase 1 Deficiency has been submitted to and successfully validated by the EMA. The MAA was submitted by Immedica Pharma AB, our commercialization partner in Europe and the Middle East. Although we submitted our BLA to the FDA to support approval for pegzilarginase based on the results of PEACE Phase 3 trial, on June 2, 2022, we announced that we received a RTF Letter from the FDA regarding our BLA submission. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. The FDA has noted that, while the data presented in the PEACE Phase 3 trial overall appeared promising and hypothesis-generating, it disagreed that the efficacy results provide substantial evidence of effectiveness for pegzilarginase. The FDA also previously reiterated the need to generate evidence of effectiveness of the product candidate through an additional randomized placebo-controlled trial of a duration longer than 24 weeks given that efficacy data based on effort-dependent clinical outcome assessments and related endpoints have a high potential for bias. We may choose not to resubmit the BLA to the FDA. If we re-submit a BLA, the FDA may again decide not to file our BLA or approve the BLA in a timely manner, or at all. If the FDA does not file or approve our BLA, we may need to conduct additional studies and our expected timing of commercialization of pegzilarginase could be delayed, or we may never commercialize pegzilarginase.

We have in the past had to cease clinical development of a product candidate for another indication. For example, we discontinued clinical development of pegzilarginase for the treatment of the hematological malignancies acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS, in December 2017 due to lack of evidence of clinical benefit. Additionally, we completed our Phase 1 clinical trial of pegzilarginase for the treatment of advanced solid tumors to study small cell lung cancer, uveal melanoma, and cutaneous melanoma and our combination trial of pegzilarginase with pembrolizumab for the treatment of patients with SCLC. Such a discontinuation as in our prior oncology program may result in longer development times, larger trials and a greater likelihood of terminating the trial or not obtaining regulatory approval.

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

We have invested a significant portion of our efforts and financial resources in the nonclinical and clinical development and testing of pegzilarginase for the treatment of patients with Arginase 1 Deficiency and in certain oncology trials and pegtarviliase for the treatment of Homocystinuria. Our ability to generate product revenues, if ever, will depend heavily on the successful development and commercialization of pegtarviliase and pegzilarginase. The success of pegtarviliase, pegzilarginase, and our other product candidates will depend on many factors, including the following:

- receiving required regulatory approvals for the development and commercialization of our product candidates as monotherapy or in combination with other products;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our product candidates and their components;
- enforcing and defending intellectual property rights and claims;
- achieving desirable therapeutic properties for our product candidates' intended indications;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with third parties;
- acceptance of our product candidates, if and when approved, by patients, the medical community and third-party payors;

- effectively competing with other therapies; and
- maintaining an acceptable safety profile of our product candidates through clinical trials and following regulatory approval.

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

***The results from our global pivotal PEACE Phase 3 trial may not support marketing approval, and the FDA or other regulatory authorities may require us to conduct additional non-clinical studies or clinical trials to evaluate subjects for an additional follow-up period.***

We announced updated data from our ongoing PEACE Phase 3 trial in December 2021 and additional data in April 2022, and submitted a BLA to the FDA seeking full approval of pegzilarginase. On June 2, 2022, we reported that we received a RTF Letter from the FDA regarding the BLA. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls. Even though the PEACE Phase 3 trial achieved statistical significance on its primary endpoint and a positive trend in a component of the key secondary endpoint was observed, nominal statistical significance was not reached on any of the prespecified key secondary or secondary endpoints evaluating motor assessments. Even if we re-submit a BLA and the FDA files our BLA, the FDA may not conclude that the design of or results seen in the trial sufficiently demonstrate substantial evidence of effectiveness, including the demonstration of a clinically meaningful effect. The FDA also weighs the benefits of a product against its risks and the FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. We cannot predict whether any BLA we may submit in the future for pegzilarginase will be filed or approved in a timely manner or at all.

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

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

The results of nonclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials that will likely differ in design and size from early-stage clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, while we have observed a reduction in blood arginine and arginine metabolite levels due to administration of pegzilarginase in patients with Arginase 1 Deficiency, and a reduction in blood arginine levels due to pegzilarginase in patients with advanced solid tumors, these data may not necessarily be predictive of the final results of all patients treated with pegzilarginase, and may also not be predictive of pegzilarginase's ability to reduce arginine or arginine metabolite levels for these patients over a longer term nor predictive of positive clinical outcomes. In addition, while we intend to announce interim data from our clinical trials from time to time, such reports may be based on unaudited data provided by our clinical trial investigators. An audit or subsequent review of this data may change the conclusions drawn from this unaudited data provided by our clinical trial investigators indicating less promising results than we anticipate. In addition, our observations of clinical improvements, through clinician and assessor feedback or assessment tools in the Phase 1/2 clinical trial, the Phase 2 open-label study, the PEACE Phase 3 clinical trial and its open-label extension of pegzilarginase in patients with Arginase 1 Deficiency after cumulative doses, may not be representative of our observations with subsequently dosed patients out to a similar or longer duration of cumulative dosing.

We completed enrollment in our single, global pivotal PEACE Phase 3 clinical trial to evaluate the safety and efficacy of pegzilarginase in patients with Arginase 1 Deficiency. Due to COVID-19, all of our clinical trial sites temporarily suspended screening, limiting patient access, and resulting in some missed dosing appointments for patients. All patients that had initially paused dosing due to COVID-19 had restarted treatment by September 2020. In addition, while we initiated dosing in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, and began dosing in the third cohort in October 2022, the timing of continued enrollment may be delayed in the future. Additionally, missed doses by patients in our clinical studies may adversely affect the usefulness of the data collected in those trials.

It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval.

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

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

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

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

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

We do not know whether any of our planned or current nonclinical studies, or ongoing or planned clinical trials, will need to be restructured or will be completed on schedule, or at all. For example, in June 2017, we delayed enrollment of pediatric patients in our Phase 1/2 clinical trial of pegzilarginase for the treatment of Arginase 1 Deficiency due to a difference in opinion with the FDA on data required to support inclusion of pediatric patients. Although we reached an agreement with the FDA in November 2017 and began dosing pediatric patients, the FDA may require additional information or studies to be conducted, or impose conditions that could further delay or restrict our other planned clinical activities in the future. Similarly, in October 2022, we received a letter from the FDA regarding a protocol amendment for our Phase 1/2 clinical rial of pegtarviliase in which the FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less an 18 years of age. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. We began our global pivotal PEACE Phase 3 clinical trial in which we are studying plasma arginine reduction from baseline over 24 weeks as our primary endpoint. However, evidence of stabilization or improvement of clinical signs and symptoms of Arginase 1 Deficiency, such as our secondary endpoints, consisting of clinical outcome assessments focused primarily on mobility, as well as clinician and caregiver global impressions of effectiveness, may be required in addition to the primary endpoint to support approval. Certain of our clinical outcome secondary endpoints are being measured using motor assessments that have not been previously validated for Arginase 1 Deficiency, including the gross motor function classification system. Such motor assessments have only been validated in ambulatory children with cerebral palsy. We believe these motor functional assessments are translatable to Arginase 1 Deficiency patients given the similarities in symptoms of children with cerebral palsy and the Arginase 1 Deficiency populations, however the FDA or other Health Authorities may disagree. For example, on June 2, 2022, we reported that we received a RTF Letter from the FDA regarding our BLA submission for pegzilarginase. In the RTF Letter, the FDA requested additional data to support effectiveness and additional information relating to Chemistry Manufacturing and Controls.

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.

***The outbreak of the novel strain of coronavirus, SARS-CoV-2 and its variants, which causes COVID-19, has, and may continue to, adversely impact our business, including supply chain interruptions, and delays for raw materials.***

Public health crises such as pandemics or similar outbreaks could adversely impact our business. Timely enrollment in our clinical trials is dependent upon global clinical trial sites which may be adversely affected by global health matters,

such as pandemics. We are currently conducting clinical trials for our product candidates in many countries, including the United States, Canada, Australia, United Kingdom and throughout the European Union. The regions in which we operate are currently being or may in the future be affected by COVID-19.

As a result of the COVID-19 outbreak, or similar pandemics, we have experienced and may continue to experience disruptions that could severely impact our business, clinical trials and nonclinical studies, including:

- delays or disruptions in nonclinical experiments and supplies for such experiments, including animals required for such experiments;
- delays or disruptions in investigational new drug application-enabling good laboratory practice standard toxicology studies due to unforeseen circumstances in our supply chain;
- increased rates of patients missing dosing appointments or withdrawing from our clinical trials following enrollment as a result of contracting COVID-19, being forced to quarantine, and other travel restrictions, or not accepting home health visits and such missed doses by patients may adversely affect the usefulness of the data collected in our trials;
- interruption of key clinical trial activities, such as clinical assessments at pre-specified timepoints during the trial and clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal, state, or foreign governments, employers and others or interruption of clinical trial subject visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of subject data and clinical study endpoints;
- interruption of, or delays in receiving, supplies of our product candidates from our CMOs due to staffing shortages, production slowdowns or stoppages, disruptions in delivery systems; and
- delays and interruptions to the supply chain, including the raw materials and other supplies needed for analysis and manufacturing of our product candidates.

The trading prices for our common stock and other biopharmaceutical companies, as well as the broader equity and debt markets, have been highly volatile as a result of the COVID-19 pandemic and the resulting impact on economic activity. The COVID-19 pandemic has also contributed to other macroeconomic conditions, including rising interest rates, inflation and potential recessions. As a result, we may face difficulties raising capital when needed, and any sales may be on unfavorable terms to us. Further, to the extent we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of existing stockholders will be diluted.

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

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

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

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

enzyme products, or that the data generated in these trials will be acceptable to the FDA or another applicable regulatory authority to support marketing approval.

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

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

We are also conducting a Phase 1/2 trial of pegtarviliase for the treatment of patients with Classical Homocystinuria. We have also completed the global pivotal PEACE Phase 3 trial and a Phase 1/2 clinical trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency. Pegzilarginase is continuing to be evaluated in an open-label extension study for patients with Arginase 1 Deficiency that participated in our previous clinical trials. Given the nature of the patient populations enrolled in these trials, we have observed and expect to continue to observe serious adverse events that could be related or unrelated to pegzilarginase and could impact the safety or efficacy of pegzilarginase and we may observe serious adverse events that could be related or unrelated to pegtarviliase and could impact the safety or efficacy of pegtarviliase. We have also dosed, and may continue to dose, patients with pegzilarginase following compassionate use requests. While such patients are not monitored as part of our ongoing clinical trials, the occurrence of significant adverse events in such patients may negatively impact the prospects of our programs.

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

In a completed Phase 1/2 clinical trial and the PEACE Phase 3 clinical trial of pegzilarginase for the treatment of patients with Arginase 1 Deficiency, we have observed serious adverse events in some patients, including hyperammonemia, hypersensitivity, and vomiting, which were infrequent, expected and manageable. Hyperammonemia is an important metabolic effect experienced by some patients with Arginase 1 Deficiency. None of the patients in these trials discontinued due to adverse events, while three patients discontinued for non-medical reasons.

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

Certain COVID-19 vaccines include pegylated components, which could result in the development of anti-PEG antibodies in vaccinated patients. Whether such antibodies have been developed, and their potential impact on the efficacy and safety of our product candidates is highly uncertain and cannot be predicted.

Testing in animals, such as our primate studies for pegtarviliase and pegzilarginase may not uncover all side effects in humans or any observed side effects in animals may be more severe in humans. For example, it is possible that patients' immune systems may recognize our engineered human enzymes as foreign and trigger an immune response, including the production of anti-drug antibodies that could limit the activity of our human enzymes. We believe this risk may be heightened in patients with deficiencies in the enzyme activity our potential therapies are intended to correct, including patients with Arginase 1 Deficiency that we are treating with pegzilarginase in our open-label extension study, and any future clinical trials we conduct for this rare genetic disease. The risk of a patient developing an immune response, including anti-drug antibodies to our engineered enzymes, and the potential impact of the immune response on the efficacy and safety of our

product candidates, cannot be predicted. In addition, our product candidates such as pegtarviliase and pegzilarginase break down target amino acids, thereby releasing metabolites 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 pegtarviliase and pegzilarginase are engineered from the human genome, pegtarviliase and pegzilarginase are produced in E. coli. This manufacturing process could lead to the products being more likely to trigger an immune response than we expect.

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

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

***Delays or difficulties in the enrollment of patients in our ongoing or planned clinical trials, could delay or prevent our receipt of necessary regulatory approvals.***

We may not be able to initiate or continue our ongoing or planned clinical trials if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the Health Authorities. For example, we are currently enrolling in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria, the timing of which has been impacted by COVID-19. While we initiated dosing in our Phase 1/2 clinical trial investigating pegtarviliase for the treatment of Classical Homocystinuria in June 2021, and reported in November 2022 that dosing of two patients in the third cohort was complete, the timing of continued enrollment may be delayed in the future. Further, we previously submitted a protocol amendment for our Phase 1/2 clinical trial of pegtarviliase, which, among other things, requested the inclusion of adolescent patients at clinical trial sites in the United States. The FDA stated the protocol did not provide adequate justification and evidence to support the prospect of direct clinical benefit for pediatric patients and placed the trial on partial clinical hold for the enrollment of patients less than 18 years of age under this IND at this time. A local Australian ethics committee, responsible for two clinical trial sites, recently stated that it would like to align with the FDA and place a hold on the enrollment of pediatric participants at those sites. Furthermore, many of our product candidates, including pegtarviliase and pegzilarginase, initially target indications that may be characterized as orphan markets, which can prolong the clinical trial timeline if sufficient patients cannot be enrolled in a timely manner. Arginase 1 Deficiency is a rare disorder, and there are no published reports of disease prevalence.

Based on an internal analysis of published literature and other data sources, we estimate the prevalence of Classical Homocystinuria to be approximately 30,000 in global addressable markets, with 80% of those patients being potential treatment candidates due to their inability to control tHcy levels with currently available treatments. Of the approximately 25,000 treatment candidates in global addressable markets, including B6-non-responsive and B6-partially-responsive patients, approximately 8,500 are estimated in the key commercial markets of the United States, France, Germany, Italy, Spain, and the United Kingdom. However, we may not be able to continue to enroll the trial as expected or locate and enroll a sufficient number of eligible patients as required by the Health Authorities, and the necessary regulatory approvals could be delayed or prevented.

We commissioned a genetic prevalence analysis and based on that analysis estimate the Arginase 1 Deficiency population is greater than 2,500 patients in the global addressable markets and greater than 1,150 patients in the territories with regulatory and launch plans underway. The genetic prevalence-based methodology is intended to account for misdiagnosis of the disease and to address limitations in newborn screening methodology, including naturally low arginine levels in newborns and lack of geographic availability or standardization of testing. Presently, only 34 U.S. states (plus the District of Columbia) perform newborn screening for Arginase 1 Deficiency, and newborn screening is not currently widely performed in European countries.

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;
- our commercialization strategy;
- 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;
- the proximity and availability of clinical trial sites for prospective patients; and
- the impact of COVID-19 or another epidemic or pandemic and related local restrictions.

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

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

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

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

***Even though we have obtained orphan drug designation for pegtarviliase in the United States and Europe for the treatment of patients with Homocystinuria and for pegzilarginase in the United States and Europe for the treatment of Arginase 1 Deficiency (hyperargininemia), we may not obtain or maintain orphan drug exclusivity for pegtarviliase or pegzilarginase and we may not obtain orphan drug designation or exclusivity for any of our other product candidates or indications.***

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

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same drug for the same disease during that time period. The applicable period is seven years in the United States and ten years in the European Union. The European Union 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.

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

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

Under the Rare Pediatric Disease Priority Review Voucher Program, upon the approval of a qualifying BLA or NDA for the treatment of a rare pediatric disease, the sponsor of such an application would be awarded a transferable rare pediatric disease priority review voucher that can be used to obtain priority review for a subsequent BLA or NDA. In September 2018, the FDA notified us that we obtained Rare Pediatric Disease designation for pegzilarginase for the treatment of patients with Arginase 1 Deficiency, and in November 2020, the FDA notified us that we obtained Rare Pediatric Disease designation for pegtarviliase for the treatment of Homocystinuria. On December 27, 2020, the Creating Hope Reauthorization Act extended the Rare Pediatric Disease Priority Review Voucher Program, and after September 30, 2024, the FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease priority review vouchers. However, there is no guarantee that any of our product candidates will be approved by that date, or at all, and, therefore, we may not be in a position to obtain a priority review voucher prior to expiration of the program, unless Congress further reauthorizes the program. Additionally,

designation of a drug for a rare pediatric disease does not guarantee that a BLA will meet the other eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Finally, a Rare Pediatric Disease designation does not necessarily lead to faster development or regulatory review of the product, or increase the likelihood that it will receive marketing approval.

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

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

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

In developing a product candidate for some indications, we may decide to use a biomarker-based test to identify patients for enrollment and, or, monitor patients in clinical trials or in the commercial environment, which could require development of new and/or modification of existing biochemical monitoring approaches. In such case, the FDA may require the development and regulatory approval of a companion diagnostic assay as a condition to approval of the product candidate. Alternatively, there may be clinical benefits for some enzyme-based therapies in enhancing currently available biochemical monitoring approaches. While we are not aware of any precedents requiring such approaches for regulatory approval, the FDA or other regulatory authorities could request that new biochemical monitoring approaches are available to support some product candidates. Clinical trials that utilize a biomarker-based test to select patients are likely to take longer and require additional funding. We do not have experience or capabilities in developing or commercializing these companion diagnostics and plan to rely in large part on third parties to perform these functions. Some 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 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, a delay in the development of the assay, or the delay or failure to obtain regulatory approval of the companion diagnostic would delay or prevent the approval of the therapeutic product candidate. Alternatively, we may also make the decision that our therapy does not require a companion diagnostic, however the Health Authorities may disagree and require the development and regulatory approval of a companion diagnostic assay as a condition of approval of the product candidate, creating additional costs and a delay in bringing our product candidate to market.

***We may in the future expand our development and regulatory capabilities and potentially implement commercialization capabilities, and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

If we seek to expand our development and regulatory capabilities in the future, we will need to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of product candidate development and regulatory affairs. Further, if any of our product candidates receives marketing approval, we would need to expand operations with respect to sales, marketing, access, reimbursement, and distribution.

We currently do not have a fully integrated commercial team to distribute and market our product candidates following regulatory approval, if approved. 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 a fully integrated commercial organization with technical expertise and supporting distribution capabilities to commercialize our product candidates in certain markets, which will be expensive and time consuming and will require significant attention of our executive officers to manage. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain commercial personnel in such markets. Any failure or delay in the development of our internal sales, marketing, access, reimbursement, 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. In particular, we have and expect to continue to partner with third parties to commercialize pegzilarginase outside the United States. For example, in March 2021, we entered into a licensing agreement with Immedica, in which Immedica acquired the product rights for commercialization of pegzilarginase in the European Economic Area and certain Middle East jurisdictions. We may have little or no control over the marketing and sales efforts of such third parties and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. If we are unable to enter into such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

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

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

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

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

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

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

**Risks Related to Commercialization**

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

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

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

Even if any of our product candidates receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success. Current treatments for Homocystinuria include CYSTADANE® (betaine anhydrous for oral solution) and dietary restrictions. Current treatments for Arginase 1 Deficiency included dietary restrictions 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 ability of healthcare professionals to accurately identify and diagnose patients with the relevant/indicated condition;
- the strength of marketing and distribution support;
- the availability of third-party payor 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 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 anticipate a competitive landscape in Homocystinuria. There is currently one FDA-approved therapy for the treatment of Homocystinuria and multiple medical foods. CYSTADANE® (betaine anhydrous for oral solution) was approved by the FDA in 1996 and is currently marketed in North America by Recordati Rare Diseases Inc. We are also aware of two investigational therapies in clinical development for the treatment of Homocystinuria. Travere Therapeutics Inc. is focused on the development of pegtibatinase, an enzyme replacement therapy in patients with Homocystinuria due to cystathionine β-synthase deficiency. Travere released topline data in December 2021 from its Phase 1/2 study of pegtibatinase which showed a 55% reduction in homocysteine at the highest dose cohort (1.5mg/kg, 2x/week). In January 2023, Travere stated that enrollment had been completed in the final cohort of their ongoing Phase 1/2 study and that the company is preparing for the initiation of a pivotal Phase 3 trial in the second half of 2023. SYNB1353 from Synlogic Inc. is also in clinical development for the potential treatment of Homocystinuria. In January 2023, the company announced completion of a Phase 1 study with anticipated advancement into Phase 2 in 2023. This investigational agent is an oral synthetic biotic platform that consumes methionine, an essential amino acid and precursor of homocysteine, in the gastrointestinal tract. We are also aware of two investigational therapies in preclinical development. The first is CDX-6512, an oral methionine-gamma-lyase enzyme therapy from Codexis. Additionally, Erytech Pharma SA also has a product candidate for Homocystinuria in preclinical development. It is possible that competitors may produce, develop, and commercialize therapeutics, or utilize other approaches to treat Homocystinuria.

There are multiple approved treatments and investigational therapies for the management of hyperammonemia commonly experienced by patients with urea cycle disorders. While these products – known as ammonia scavengers – do not target the core metabolic defect of Arginase 1 Deficiency, they can help patients manage their elevated ammonia levels. There are multiple marketed therapies to treat hyperammonemia associated with urea cycle disorders. Those include RAVICTI® (glycerol phenylbutyrate) and BUPHENYL® (sodium phenylbutyrate) from Horizon Therapeutics plc and OLPRUVA™ (sodium phenylbutyrate) from Acer Therapeutics Inc.; additionally, at least one generic formulation of sodium phenylbutyrate is commercially available. We are aware of one other company with an investigational therapy for Arginase 1 Deficiency in preclinical stages, Erytech Pharma SA, who in February 2022 announced the allowance of a U.S. patent application covering arginine deiminase encapsulated into red blood cells for the treatment of Arginase 1 Deficiency.

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 sufficiently differentiated from other products in the market;
- attract qualified management, scientific, product development and commercial personnel;
- obtain and maintain patent and/or other proprietary protection for our product candidates and technologies;
- obtain required regulatory approvals;
- successfully launch and commercialize our approved products; 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 patients, physicians, or third-party payors to accept our product candidates.

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/or safety to establish a meaningfully differentiated value proposition for patients, physicians, and third-party payors. 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, marketing, and market access 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 United Kingdom and the countries of the European Union, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In general, the prices of products under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

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

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

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

With the enactment of the Biologics Price Competition and Innovation Act of 2009, or BPCIA, an abbreviated pathway for the approval of biosimilar biological products (both highly similar and interchangeable biological products) was created. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing reference product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the first licensure of date of the reference product licensed under a BLA. On March 6, 2015, the FDA approved the first biosimilar product under the BPCIA and on July 28, 2021, approved the first interchangeable biosimilar.

A biological product submitted for licensure under a BLA is eligible for a period of exclusivity that commences on the date of its licensure, unless its date of licensure is not considered a date of first licensure because it falls within an exclusion under the BPCIA. There is a risk that this exclusivity could be shortened due to congressional action or otherwise, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not apply to companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Most states have enacted substitution laws that permit substitution of only interchangeable biosimilars. The extent to which a 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.

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

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

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

***If in the future we are unable to establish U.S. or global sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if they are approved, thus limiting our ability to generate any product revenue.***

We do not yet have a fully integrated commercial organization with all of the functions required to market, sell and distribute our product candidates that may receive regulatory approval. In order to commercialize any product candidates after approval, 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 may decide 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. In particular, we have and expect to continue to partner with third parties to commercialize pegzilarginase outside the United States. In March 2021, we entered into a license and supply agreement with Immedica, in which Immedica acquired the product rights for commercialization of pegzilarginase for certain territories outside the U.S. If we are unable to enter into or maintain 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.

***If we obtain approval to commercialize our product candidates outside of the United States, in particular in the European Union, a variety of risks associated with international operations could materially adversely affect our business.***

We expect that we will be subject to additional risks in commercializing our product candidates outside the United States, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- different processes and requirements to obtain adequate reimbursement for our approved therapies;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods, fires or public health crises, pandemics, and epidemics, such as COVID-19.

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

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

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

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

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

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

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

We do not own or operate facilities for the manufacture of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. For example, we currently rely on third party contract manufacturing organizations to manufacture and supply nonclinical and clinical trial quantities of our product candidates pegtarviliase and pegzilarginase, and for additional pipeline product candidates. We also expect to continue to rely on such third parties to manufacture pegtarviliase for our clinical trials and to manufacture and supply clinical and commercial quantities of pegzilarginase.

We rely, and expect to continue to rely, on third parties, for the manufacture of our product candidates for nonclinical studies and for our existing and future planned clinical trials. We also expect to rely on third parties for commercial manufacture if any of our product candidates receive marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts.

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

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

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

- the possible noncompliance by the third party with regulatory requirements and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the operations of such third parties could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of such party, the issuance of an FDA Form 483 notice or warning letter or other enforcement action by the FDA or other regulatory authority;

- delays due to production shortages resulting from any events affecting supply or manufacturing capabilities domestically and abroad;
- delays due to the malfunction or non-performance of manufacturing equipment resulting in failed manufacturing runs or the production of materials that do not meet quality standards;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

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

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

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

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

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

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

We do not plan to internally develop diagnostics or monitoring assays, or Assays. As a result, we are dependent on the efforts of our third-party strategic partners to successfully commercialize any needed Assays. Our strategic partners:

- may not perform their obligations as expected;
- may encounter production difficulties that could constrain the supply of the Assays;
- may have difficulties gaining acceptance of the use of the Assays in the clinical community;
- may not pursue commercialization of any Assays;
- 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 Assay product candidates; and
- may terminate their relationship with us.

If Assays needed for use with our therapeutic product candidates fail to gain market acceptance, our ability to derive revenues from sales of these therapeutic product candidates could be harmed. If our strategic partners fail to develop and commercialize these Assays, 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 or commercialization of certain of our product candidates.***

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 also have entered into and expect to enter into future partnership agreements to commercialize pegzilarginase outside the United States, including through our licensing agreement with Immedica. 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 or license and development 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 a 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, or our existing or future partners are not able to adequately fund their development or commercialization activities pursuant to our arrangements, 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.

***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.

**Risks Related to Government Regulation**

***If there are delays in obtaining, or we are not able to obtain, 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, by the EMA pursuant to an MAA, and by other comparable regulatory authorities outside the United States prior to commercialization. The process of obtaining marketing approvals, both in the United States and internationally, is expensive and takes many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval in Europe or another non-U.S. jurisdiction may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our third-party strategic partners may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all.

Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. Furthermore, the implementation of Brexit may disrupt the operation of any pre-and post-authorization clinical trial infrastructure and regulatory frameworks in Europe, as discussed further below. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our product candidates in any market.

Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing marketing approval requires the submission of extensive nonclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional nonclinical, clinical or other studies. In addition, varying interpretations of the data obtained from nonclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may also cause delays in or prevent the approval of an application.

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

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

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

Additionally, the implementation of the United Kingdom's exit from the European Union, or "Brexit," may cause disruptions and uncertainty in the current regulatory framework in Europe. Brexit has resulted in the EMA moving from the United Kingdom to the Netherlands. In the United Kingdom, this transition may cause disruption in the administrative and medical scientific links between the EMA and MHRA. Following the United Kingdom's departure from the European Union, it no longer automatically complies with the standards of clinical efficacy, safety and chemistry control, and manufacture as applied by the European Medicines Directive. Applications submitted for marketing authorization under the centralized EMA procedure will no longer be automatically validated for authorization in the United Kingdom, and the benefit-risk assessments conducted by the United Kingdom may not be consistent with the EMA conclusions. The cumulative effects

of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the European Union and/or the United Kingdom. In view of the current lack of detail and resolution with regard to the Brexit transition, we are unable to confidently predict the effects of such disruption to the regulatory framework in Europe, and as to how this may delay or impair any potential regulatory approvals, commercialization of any of our product candidates, and our ability to generate potential revenues. If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

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

We have received Fast Track Designation from the FDA for our product candidate pegtarviliase for the treatment of Homocystinuria and for our product candidate pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency and may seek such designation for some or all of our other 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 pegtarviliase for the treatment of Homocystinuria and for pegzilarginase for the treatment of hyperargininemia secondary to Arginase 1 Deficiency, and even if we receive Fast Track Designation for other product candidates or indications in the future, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many drugs or biologics that have received Fast Track Designation have failed to obtain approval.

***The FDA may consider approval of our products through the use of the accelerated approval program, but such mechanism may not lead to a faster development or regulatory review or approval process. Even if we receive approval from the FDA under the accelerated approval program, if our confirmatory postmarketing trial does not verify clinical benefit, or if we do not comply with rigorous postmarketing requirements, the FDA may seek to withdraw the approval.***

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 is thought to predict clinical benefit but is not itself a measure of clinical benefit, or a biomarker that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be adequate and well controlled as required by the FDC Act.

If the FDA were to consider accelerated approval in the review of an application for any product candidates, the FDA may determine there is inadequate justification to support that our surrogate endpoint is reasonably likely to predict clinical benefit in patients.

For drugs or biologics granted accelerated approval, post-marketing well-controlled, adequately powered confirmatory trials of sufficient duration are typically 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 the FDA could require that the trial be designed, initiated, and/or fully enrolled at the time of BLA submission. 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.

Recently, the accelerated approval pathway has come under scrutiny within the FDA and by Congress. The FDA has put increased focus on ensuring that confirmatory studies are conducted with diligence and, ultimately, that such studies confirm the benefit of the approved product, and Congress has considered various proposals to make changes to the accelerated approval pathway. The Food and Drug Omnibus Reform Act, or FDORA, was recently enacted, which included provisions related to the accelerated approval pathway. Pursuant to FDORA, the FDA is authorized to require a post-approval study to be underway prior to approval or within a specified time period following approval. FDORA also requires the FDA to specify conditions of any required post-approval study, which may include milestones such as a target date of study completion and requires sponsors to submit progress reports for required post-approval studies and any conditions required by the FDA not later than 180 days following approval and not less frequently than every 180 days thereafter until completion or termination of the study. FDORA enables the FDA to initiate criminal prosecutions for the failure to conduct with due diligence a required post-approval study, including a failure to meet any required conditions specified by the FDA or to submit timely reports.

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

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

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

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

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

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

Our product candidates and the activities associated with their development and commercialization, including their testing, manufacture, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP, requirements relating to

manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, including periodic inspections by the FDA and other regulatory authorities, requirements regarding the distribution of samples to physicians and recordkeeping.

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

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

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

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

Non-compliance with European requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with European and certain U.S. state 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, physician assistants, certain nurses, and teaching hospitals, which includes annual data collection and reporting obligations, with reported information disclosed on a searchable website on an annual basis; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

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

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

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

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

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

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The ACA, among other things, also expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program and imposed a significant annual, nondeductible fee on companies that manufacture or import certain branded prescription drug products.

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. These reductions went into effect in 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2031, with the exception of a temporary suspension and reduction implemented under various COVID-19 relief legislation through June 30, 2022, unless additional Congressional action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On January 20, 2017, federal agencies with authorities and responsibilities under the ACA were directed to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. More recently, the Tax Cuts and Jobs Act was signed into law, which eliminated certain requirements of the ACA, including the individual mandate. On June 17, 2021, the United States Supreme Court held that plaintiffs do not have standing to challenge the constitutionality of the individual mandate. It is unclear whether there will be additional challenges to the ACA. Additionally, on January 28, 2021, the President of the United States issued an executive order to initiate a special enrollment period from February 15, 2021 through May 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is uncertain how other such litigation or the healthcare measures of the United States administration will impact the ACA and our business.

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. For example, on September 9, 2021, the Biden administration published a wide-ranging list of policy proposals to lower prescription drug prices, including by allowing Medicare to negotiate prices and disincentivizing price increases, and to support market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase price transparency. These initiatives recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which will, among other things, allow the U.S. Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D, although this will only apply to high-expenditure single-source drugs that have been approved for at least 7 years (11 years for biologics). The negotiated prices will first become effective in 2026 and will be capped at a statutory ceiling price. The IRA will also, beginning in October 2023, penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. In addition, the law eliminates the "donut hole" under Medicare Part D beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and requiring manufacturers to subsidize, through a newly established manufacturer discount program, 10% of Part D enrollees' prescription costs for brand drugs below the out-of-pocket maximum and 20% once the out-of-pocket maximum has been reached. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. The

implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our product candidates.

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

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

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business and financial condition. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the 2017 Tax Cuts and Jobs Act, among others, reduced the orphan drug credit from 50% to 25% of qualifying expenditures. When and if we become profitable, this reduction in tax credits may result in an increased federal income tax burden on our orphan drug programs. On March 27, 2020, the Coronavirus Aid, Relief and Economic Security, or CARES Act, was enacted and modified certain portions of the 2017 Tax Cuts and Jobs Act, including with respect to the carryforward of net operating losses. Future changes in corporate tax rates, rules relating to the realization of net deferred tax assets, and other tax legislation could have a material impact on the value of our deferred tax assets, could result in a significant one-time charges, and could increase our future U.S. tax expense.

**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 diagnostic developed by us or a third-party strategic partner. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates and rely on our licensors to obtain patent protection for our licensed intellectual property. Our patent portfolio includes patents and patent applications we own or we exclusively license from the University of Texas at Austin. This patent portfolio includes issued patents and pending patent applications covering compositions of matter and methods of use.

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

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. The U.S. Patent and Trademark Office, or U.S. PTO, has not established a consistent policy regarding the breadth of claims that it will allow in biotechnology patents. In addition, the laws of foreign jurisdictions may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications

in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions, nor can we know whether those from whom we license patents were the first to make the inventions claimed or were the first to file. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and product candidates. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, during prosecution of any patent application, the issuance of any patents based on an application may depend upon our ability to generate additional nonclinical or clinical data that supports the patentability of our proposed claims. We may not be able to generate such data on a timely basis, to the satisfaction of the U.S. PTO, or at all.

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

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

The issuance of a patent, while given the presumption of validity under the law, is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or 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. The U.S. PTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, we also rely on licensors to effect such payments with respect to the patents and patent applications that we in-license. Moreover, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

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

Our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. We may become party to, or threatened with, future adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference or derivation proceedings before the U.S. PTO and similar bodies in other jurisdictions. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. We may also institute proceedings in courts or patent offices seeking decisions regarding the validity or scope of patents owned by third parties.

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

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

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

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

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

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

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

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

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

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

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

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and/or management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the market price of our common stock. In some cases, we may choose not to pursue litigation against those that have infringed on our patents, or used them without authorization, due to the associated expenses and time commitment of monitoring these activities. If we fail to protect or to enforce our intellectual property rights successfully, our competitive position could suffer, which could harm our results of operations.

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

Presently we have rights to intellectual property to develop our product candidates, including patents and patent applications we own or exclusively license from the University of Texas at Austin. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-

party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

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

We rely on trade secret protection to protect our interests in proprietary know-how and in processes that are unpatentable or for which patents are difficult to obtain or enforce. We may not be able to protect our trade secrets adequately. We have a policy of requiring our consultants, advisors and strategic partners to enter into confidentiality agreements and our employees to enter into invention, non-disclosure and non-compete agreements. However, no assurance can be given that we have entered into appropriate agreements with all parties that have had access to our trade secrets, know-how or other proprietary information, or that such agreements will provide for a meaningful protection of our trade secrets, know-how or other proprietary information in the event of any unauthorized use or disclosure of information. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. Even if we are successful in prosecuting such claims, any remedy awarded may be insufficient to fully compensate us for the improper disclosure or misappropriation. Furthermore, although we seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems, it is also possible that our trade secrets, know-how or other proprietary information could be obtained by third parties as a result of breaches of such systems.

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

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

Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and our patent rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly developing countries. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

As part of ordinary course prosecution and maintenance activities, we determine whether to seek patent protection outside the United States and in which countries. This also applies to patents we have acquired or in-licensed from third parties. In some cases, this means that we, or our predecessors in interest or licensors of patents within our portfolio, have sought patent protection in a limited number of countries for patents covering our product candidates. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and, even in jurisdictions where we have or are able to obtain issued patents, our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful.

In addition, certain countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we may have limited remedies if our patents are infringed or if we are compelled to grant a license to our patents to a third party, which could materially diminish the value of those patents. In addition, there may be patent law reforms in foreign jurisdictions that could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents in those foreign jurisdictions. This could limit our potential revenue opportunities.

Accordingly, our efforts to obtain, register, and enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license. Moreover, patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

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

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

In December 2013, our wholly owned subsidiaries AECase, Inc. and AEMase, Inc. each entered into an exclusive, worldwide license agreement, including the right to grant sublicenses, with the University of Texas at Austin for certain intellectual property owned by the University of Texas at Austin related to our program candidates related to cystinase and methioninase. In January 2017, we and the University of Texas at Austin entered into an Amended and Restated Patent License Agreement, or the Restated License, which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us. The Restated License was amended in August 2017, December 2017, and December 2018 to revise diligence milestones and license additional patent applications, including our program candidates under the pegtarviliase and Cystinuria programs. The intellectual property licensed under the Restated License includes inventions that were 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 or may develop drug candidates for the diseases our drug candidates seek to treat that do not infringe our intellectual property rights, but which perform better or are more successful than our drug candidates;
- drug candidates covered by issued patents and other intellectual property that we hold may prove to be ineffective for their intended treatment or we may not obtain regulatory approval for such drug candidates;
- we or our licensors or collaborators might not have been the first to make the inventions covered by an issued patent or pending patent application that we own or license;
- we or our licensors or collaborators might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing or misappropriating our intellectual property rights;
- pending patent applications that we own or license may not lead to issued patents;
- issued patents that we own or license may not provide us with any competitive advantages, or may be narrowly construed or held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop or in-license additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

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

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

As is the case with other biotechnology companies, our success is heavily dependent on patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. Further, the United States has recently enacted patent reform legislation. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this has created greater uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

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

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one of the U.S. patents covering each of such approved product(s) or the use thereof may be eligible for up to five years of patent term restoration. Patent term extension allows a maximum of one patent to be extended per FDA-approved product. Patent term extension also may be available in certain foreign countries upon regulatory approval of our product candidates, if any. 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 or scope 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.

***We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.***

We attempt to protect our pharmaceutical developments, services, and products under trademark laws. However, our trademark applications may not be allowed for registration, and registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would.

***Third parties may pursue trademark infringement actions against us, potentially resulting in substantial costs and material delays.***

As our activities grow, we may be subject to an increasing amount of litigation that is common in the pharmaceutical industry based on allegations of infringement or other alleged violations of trademarks. Any claims of infringement, with or without merit, could be time consuming, costly, and difficult to defend. Moreover, intellectual property litigation or claims could require us to redesign packaging and advertising materials associated with our packaging, which could result in substantial costs and material delays.

**Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business**

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

We are a clinical-stage biotechnology company with a limited operating history, and, as of December 31, 2022, had 69 employees. We are highly dependent on the research and development, clinical and business development expertise of our executive officers, as well as the other principal members of our management, scientific and clinical team. Any of our management team members may terminate their employment with us at any time. We do not maintain “key person” insurance for any of our executives or other employees.

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

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

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

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to (i) comply with FDA regulations or similar regulations of comparable non-U.S. regulatory authorities, (ii) provide accurate information to the FDA or comparable non-U.S. regulatory authorities, (iii) comply with manufacturing standards we have established, (iv) comply with the Foreign Corrupt Practices Act and federal and state healthcare fraud and abuse laws and regulations and similar

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

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

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

- inability to bring a product candidate to the market;
- decreased demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- decline in our share price.

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

***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.

**Risks Related to Our Common Stock**

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

We have a concentrated stockholder base and our executive officers and directors, combined with our stockholders who, to our knowledge, each owned more than 5% of our outstanding common stock, in the aggregate, beneficially own shares representing a substantial number of our capital stock as of December 31, 2022. As a result, if these stockholders were to choose to act together, they may be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would likely 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.

***Failure to achieve and maintain effective internal control over financial reporting in accordance with Section 404 of the Sarbanes-Oxley Act could have a material adverse effect on our business and stock price.***

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain a non-accelerated filer, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles in the United States. We may encounter problems or delays in implementing any changes necessary to make a favorable assessment of our internal control over financial reporting. If we cannot favorably assess the effectiveness of our internal control over financial reporting, or if our independent registered public accounting firm is unable to provide an unqualified attestation report on our internal controls when required, investors could lose confidence in our financial information and the price of our common stock could decline.

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

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

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

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;

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

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

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

***Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, and our amended and restated bylaws designates the federal courts of the United States as the exclusive forum for actions arising under the Securities Act, each of 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.

Our restated bylaws provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (a Federal Forum Provision). Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While there can be no assurance that federal or state courts will follow the holding of the Delaware Supreme Court or determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court.

These choice of forum provisions 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 specified courts could face additional litigation costs in pursuing any such claim. The specified courts 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 these provisions of our governance documents 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 has been and may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.***

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

- the success or failure of competitive products or technologies;
- results of ongoing or planned clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- operating results that fail to meet expectations of securities analysts that cover our company;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic and market conditions including rising interest rates and inflation, as well as the possibility of a recession or further economic downturn, and the economic impact of the war in Ukraine and its potential suppler chain impacts and the ongoing COVID-19 pandemic; and
- the other factors described in this “Risk Factors” section.

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

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

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

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

Moreover, we have also registered under the Securities Act shares of common stock that we may issue under our equity compensation plans.

In July 2020, we filed a new shelf registration statement on Form S-3 that was declared effective in July 2020 by the SEC for the potential offering, issuance and sale by us of up to $400.0 million of our common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock and debt securities, subscription rights to purchase common stock and units consisting of all or some of these securities; however, for so long as the aggregate market value of our common equity held by our non-affiliates, or public float, is less than $75 million, we will only be able to sell securities with an aggregate market value of up to one-third of our public float. If we sell common stock, preferred stock, convertible securities and other equity securities in other transactions pursuant to our shelf registration statements on Form S-3, existing

investors may be materially diluted by such subsequent sales and new investors could gain rights superior to our existing stockholders. In May 2021, we filed a shelf registration statement on Form S-3, that was declared effective on June 8, 2021 by the SEC, registering up to 19,020,434 shares of our common stock held by 667, L.P., or 667, and Baker Brothers Life Sciences, L.P., or Life Sciences, and together with 667, the Baker Funds, which includes 15,610,328 shares of common stock issuable upon the exercise of pre-funded warrants held by the Baker Funds, for resale or other disposition from time to time as described in the registration statement.

In May 2022, we entered into an "at-the-market" offering of our common stock pursuant to a sales agreement between us and JonesTrading Institutional Services LLC, or JonesTrading, under a shelf registration statement on Form S-3. Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to JonesTrading at any time throughout the term of the sales agreement, which has a term equal to the term of the registration statement on Form S-3 unless otherwise terminated earlier by us or JonesTrading pursuant to the terms of the sales agreement. The number of shares that are sold by JonesTrading after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with JonesTrading. Because the price per share of each share sold pursuant to the sales agreement will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued. Issuances of any shares sold pursuant to the sales agreement will have a dilutive effect on our existing stockholders.

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

***We will not receive a significant amount, or potentially any, additional funds upon the exercise of our pre-funded warrants; however, any exercise would increase the number of shares eligible for future resale in the public market and result in substantial dilution to our stockholders.***

As of December 31, 2022, we have issued pre-funded warrants to purchase a total of 34,982,640 shares of our common stock, of which 6,091,062 have been exercised and 28,891,578 are currently outstanding. Each pre-funded warrant is exercisable for $0.0001 per share of common stock underlying such pre-funded warrant, which may be paid by way of a cashless exercise, meaning that the holder may not pay a cash purchase price upon exercise, but instead would receive upon such exercise the net number of shares of common stock determined according to the formula set forth in the pre-funded warrant. Accordingly, we will not receive a significant amount, or potentially any, additional funds upon the exercise of the pre-funded warrants. To the extent such pre-funded warrants are exercised, additional shares of common stock will be issued for nominal or no additional consideration, which will result in substantial dilution to the then existing holders of our common stock and will increase the number of shares eligible for resale in the public market. Sales of substantial numbers of such shares in the public market could adversely affect the market price of the common stock, causing our stock price to decline.

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

There is no public trading market for our pre-funded warrants issued in the February 2019, April 2020 and May 2022 public offerings, and we do not expect a market to develop. In addition, we do not intend to apply to list the pre-funded warrants on any securities exchange or nationally recognized trading system, including the Nasdaq Global Market. Without an active market, the liquidity of the pre-funded warrants will be limited and their value may be adversely impacted.

Additionally, each holder of pre-funded warrants will not be entitled to exercise any portion of any pre-funded warrant, which, upon giving effect to such exercise, would cause (i) the aggregate number of shares of our common stock beneficially owned by the holder (together with its affiliates) to exceed 4.99%, or 9.99% for certain holders, of the number of shares of our common stock outstanding immediately after giving effect to the exercise, or (ii) the combined voting power of our securities beneficially owned by the holder (together with its affiliates) to exceed 4.99%, or 9.99% for certain holders, of the combined voting power of all of our securities then outstanding immediately after giving effect to the exercise. However, any holder may increase or decrease such percentage to any other percentage (not in excess of 19.99% for the majority of such warrants) upon at least 61 days' prior notice from the holder to us.

***We are a "smaller reporting company," and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.***

We are a "smaller reporting company" under the Exchange Act. For so long as we remain a smaller reporting company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not smaller reporting companies. These exemptions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting of Section 404(b) of the Sarbanes-Oxley Act; and
- reduced disclosure obligations regarding executive compensation.

We may continue to take advantage of these exemptions until we are no longer a smaller reporting company. We will remain a smaller reporting company if we have either (i) less than $250 million in market value of our shares held by non-affiliates as of the last business day of our second fiscal quarter or (ii) less than $100 million of annual revenues in our most recent fiscal year and a market value of our shares held by non-affiliates less than $700 million as of the last business day of our second fiscal quarter. We may choose to take advantage of some but not all of these scaled disclosure requirements. Therefore, the information that we provide stockholders may be different than one might get from other public companies. Further, if some investors find our shares of common stock less attractive as a result, there may be a less active trading market for our shares of common stock and the market price of such shares of common stock may be more volatile.

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

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

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting. As discussed above, if we cease to be a non-accelerated filer, 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.

***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.

***The price of our common stock may not meet the requirements for continued listing on Nasdaq. If we fail to regain compliance with the minimum listing requirements, our common stock will be subject to delisting. Our ability to publicly or privately sell equity securities and the liquidity of our common stock could be adversely affected if our common stock is delisted.***

The continued listing standards of Nasdaq require, among other things, that the minimum bid price of a listed company's stock be at or above $1.00. If the closing minimum bid price is below $1.00 for a period of more than 30 consecutive trading days, the listed company will fail to be in compliance with Nasdaq's listing rules and, if it does not regain compliance within the grace period, will be subject to delisting. As previously reported on January 18, 2023, we received a notice from the Nasdaq Listing Qualifications Department notifying us that for 30 consecutive trading days, the bid price of our common stock had closed below the minimum $1.00 per share requirement. In accordance with Nasdaq's listing rules, we were afforded a grace period of 180 calendar days, or until July 12, 2023, to regain compliance with the bid price requirement. In order to regain compliance, the bid price of our common stock must close at a price of at least $1.00 per share for a minimum of 10 consecutive trading days.

If we fail to regain compliance by July 12, 2023, we may be eligible for a second 180 day compliance period if we elect to transfer to The Nasdaq Capital market, provided that, on such date, we meet the continued listing requirement for market value of publicly held shares and all other applicable Nasdaq listing requirements (other than the minimum closing bid price requirement) and we provide written notice to Nasdaq of our intention to cure the deficiency during the second compliance period, by effecting a reverse stock split, if necessary. Such extension of the grace period would be subject to Nasdaq's discretion, and there can be no guarantee that we would be granted an extension.

We cannot provide any guarantee that we will regain compliance during the grace period or be able to maintain compliance with Nasdaq's listing requirements in the future. If we are not able to regain compliance during the grace period, or any extension of the grace period for which we may be eligible, our common stock will be subject to delisting and "penny stock" rules. Delisting from Nasdaq could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities.

**General Risk Factors**

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

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

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

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

***Our information technology systems, or those used by our CROs, third-party vendors, contractors or consultants, may fail or suffer security breaches, cyber-attacks, and loss of data, which could harm our business, reputation, financial condition, and operations.***

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

Moreover, if a security breach affects our systems or results in the unauthorized access, use or disclosure of personal information, our reputation could be materially damaged. In addition, such a breach may require notification to governmental agencies, the media and/or affected individuals pursuant to various federal, state and international privacy and security laws, if applicable, including HIPAA or HITECH and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. We would also be exposed to a risk of loss or litigation and potential liability under laws, regulations and contracts that protect the privacy and security of personal information. For example, the California Consumer Privacy Act, or the CCPA, imposes a private right of action for security breaches that could lead to some form of remedy including regulatory scrutiny, fines, private right of action settlements, and other consequences. Additional states, including Virginia, Connecticut, Colorado, and Utah, have recently enacted privacy-related laws, and legislation is pending in many other states. The financial exposure from the events referenced above could either not be insured against or not be fully covered through any insurance that we may maintain, and there can be no assurance that the limitations of liability in any of our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages as a result of the events referenced above. Any of the foregoing could have a material adverse effect on our business, reputation, results of operations, financial condition and prospects.

***We depend on our information technology and infrastructure, and disruptions could compromise sensitive information related to our business or other personal information or prevent us from accessing critical information, which could adversely affect our business, reputation, results of operations, financial condition and prospects.***

We rely on the efficient and uninterrupted operation of information technology systems to manage our operations, to process, transmit, and store electronic and financial information, and to comply with regulatory, legal and tax requirements. We also depend on our information technology infrastructure for communications among our personnel, contractors, consultants and suppliers. System failures or outages could materially compromise our ability to perform these functions in a timely manner, which could harm our ability to conduct business or delay our financial reporting, and could otherwise compromise the security of sensitive information, including personal information and health information. In addition, our remediation efforts for system failures, outages, or security breaches may not be successful. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information, including personal information and health information. In addition, we depend on third parties to operate and support our information technology systems. Failure by these providers to adequately deliver the contracted services could have an adverse effect on our business, which in turn may materially adversely affect our operating results and financial condition.

***We are subject to a variety of stringent and changing privacy and data security laws, regulations and standards, as well as contractual obligations related to data privacy and security, and our actual or perceived failure to comply with them could harm our business and reputation and subject us to significant fines and liability.***

We maintain a quantity of sensitive information, including confidential business and patient health information in connection with our clinical trials, and are subject to laws and regulations governing the privacy and security of such information. In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws, and federal and state consumer protection laws. Each of these laws is subject to varying interpretations and constantly evolving. For example, the European Union GPDR, or the GDPR, and United Kingdom General Data Protection Regulation, or the UK GDPR, which apply extraterritorially, and impose several strict requirements for controllers and processors of personal information, including higher standards for obtaining consent from individuals to process their personal information, increased requirements pertaining to the processing of special categories of personal information (such as health information) and pseudonymized (i.e., key-coded) data, and transfer of personal information from the EEA/UK/Switzerland to countries not deemed to have adequate data protections laws (e.g., the United States as of January 1, 2023, although active treaty negotiations between the United States and the EU may change that status in 2023). The GDPR also provides that countries in the EEA may establish their own laws and regulations further restricting the processing of certain personal information, including genetic data, biometric data, and health data. Companies that must comply with the GDPR and UK GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to €20 million or £17 million (approximately $22.6 million), respectively, or four percent of the annual global revenues of the noncompliant company, whichever is greater.

In the United States, in addition to HIPAA, various federal and state regulators have adopted, or are considering adopting, laws and regulations concerning personal information and data security. Certain state laws may be more stringent or broader in scope, or offer greater individual rights, with respect to personal information than federal, international or other state laws, and such laws may differ from each other, all of which may complicate compliance efforts. For example, California, which continues to be a critical state with respect to evolving consumer privacy laws after enacting the California Consumer Privacy Act, or CCPA, later amended by ballot measure through the California Privacy Rights Act, or CPRA. The CPRA took effect in January 2023 and enforcement will begin on July 1, 2023, subject to regulations promulgated through a newly created enforcement agency called the California Privacy Protection Agency, or CPPA. Failure to comply with the CCPA and the CPRA may result in significant civil penalties, injunctive relief, or statutory or actual damages as determined by the CPPA and California Attorney General through its investigative authority. Notably, comparable consumer privacy laws are set to take effect in 2023 in other states including the Virginia Consumer Data Protection Act (effective January 1, 2023), the Colorado Privacy Act and the Connecticut Data Privacy Act (both effective July 1, 2023), and the Utah Consumer Privacy Act (effective December 31, 2023). Compliance with this new privacy legislation may result in additional costs and expense of resources to maintain compliance. There is also discussion in the United States of a new comprehensive federal data privacy law to which we would become subject if it is enacted.

We cannot provide assurance that (i) current or future legislation will not prevent us from generating or maintaining personal information, or (ii) that patients will consent to the use of their personal information (as necessary). Either of these circumstances may prevent us from undertaking or publishing essential research and development, manufacturing, and commercialization, which could have a material adverse effect on our business, results of operations, financial condition, and prospects.

Federal, state, and foreign government requirements include obligations of companies to notify regulators and/or individuals of security breaches or other similar reportable incidents experienced by us, our vendors, contractors, and organizations with whom we had specific contractual obligations to protect our data. Further, the improper access to, use of, or disclosure of our data or a third-party's personal information could subject us to individual or consumer class action litigation and governmental investigations and proceedings by federal, state, and local regulatory entities in the United States and by international regulatory entities. Compliance with these and any other applicable privacy and data security laws and regulations is a rigorous and time-intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules and possible government oversight.

In addition to government regulation, privacy advocates and industry groups have and may in the future propose self-regulatory standards from time to time. These and other industry standards may legally or contractually apply to us, or we may elect to comply with such standards. It is possible that if our practices are not consistent or viewed as not consistent with legal and regulatory requirements, including changes in laws, regulations and standards or new interpretations or

applications of existing laws, regulations and standards, we may become subject to audits, inquiries, whistleblower complaints, adverse media coverage, investigations, loss of export privileges, or severe criminal or civil sanctions, all of which may have a material adverse effect on our business, operating results, reputation, and financial condition.

All of these evolving compliance and operational requirements impose significant costs, such as costs related to organizational changes, implementing additional protection technologies, training employees and engaging consultants, which are likely to increase over time. In addition, such requirements may require us to modify our data processing practices and policies, distract management or divert resources from other initiatives and projects, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Any failure or perceived failure by us to comply with any applicable federal, state or similar foreign laws and regulations relating to data privacy and security could result in damage to our reputation, as well as proceedings or litigation by governmental agencies or other third parties, including class action privacy litigation in certain jurisdictions, which would subject us to significant fines, sanctions, awards, injunctions, penalties or judgments. Any of the foregoing could have a material adverse effect on our business, results of operations, financial condition and prospects.

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

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

***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 if they issue an adverse or misleading opinion regarding our stock, our stock price and trading volume could decline.***

If securities or industry analysts do not publish research or reports about our business, or publish negative or misleading 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.

## ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

## ITEM 2. PROPERTIES

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

## ITEM 3. LEGAL PROCEEDINGS

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

## ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

## PART II

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

#### Market Information and Holders

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

As of February 21, 2023, there were approximately 22 stockholders of record of our common stock based on information provided by our transfer agent. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

#### Dividends

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

#### Securities Authorized for Issuance under Equity Compensation Plans

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

#### Recent Sales of Unregistered Securities

None.

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

None.

### ITEM 6. [RESERVED]

## 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 on Form 10-K, or 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" refers to Aeglea BioTherapeutics, Inc. and its consolidated subsidiaries taken as a whole.*

### Overview

We are a clinical-stage biotechnology company developing human enzyme therapeutics to benefit people with rare metabolic diseases. Our vision is to redefine what was thought possible and pioneer bold science to deliver groundbreaking medicines to devastating rare diseases. Our two clinical programs are pegtarviliase for Homocystinuria and pegzilarginase for Arginase 1 Deficiency. Both clinical programs are focused on the underlying key metabolites that drive the clinical manifestations of these devastating rare metabolic diseases. We are on a mission to change lives by bringing innovative therapies to underserved rare disease communities.

Our primary focus is the advancement of pegtarviliase through clinical development, regulatory approval and into commercialization. We believe pegtarviliase has the potential to be a best-in-class enzyme therapy for the treatment of Classical Homocystinuria. Pegtarviliase is currently being studied in a Phase 1/2 clinical trial to assess safety and efficacy in patients with Classical Homocystinuria, also known as Homocystinuria due to cystathionine β-synthase deficiency. We estimate that there are approximately 30,000 Classical Homocystinuria patients in global addressable markets and we estimate about 80% of these patients are unable to control their tHcy levels to targeted clinical thresholds with the currently available treatments. With significantly elevated homocysteine levels, these patients are continuing to experience irreversible progression and remain at risk for catastrophic thromboembolic events resulting in death.

Our other clinical program is pegzilarginase for the treatment of Arginase 1 Deficiency. We reported positive topline data for pegzilarginase for our global pivotal PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial in December 2021 and are continuing to evaluate the safety of pegzilarginase in an open-label study for patients who participated in our previously completed trials. Based on the results from PEACE and a previous Phase 1/2 clinical trial, a Marketing Authorization Application, or MAA, was submitted to the European Medicines Agency, or EMA, by Immedica Pharma AB, or Immedica, our commercial partner in Europe and several countries in the Middle East. We announced in August 2022 that the MAA was validated by the EMA and is currently under review. We submitted a Biologics License Application, or BLA, to the U.S. Food and Drug Administration, or FDA, for pegzilarginase and announced in June 2022 that we had received a Refuse to File, or RTF, letter from the FDA. The FDA requested additional data to support effectiveness, such as evidence showing that plasma arginine and metabolite reduction predicts clinical benefit in patients with ARG1-D or clinical data demonstrating a treatment effect on clinically meaningful outcomes. Previously the agency had requested an additional randomized placebo-controlled trial of a duration longer than 24 weeks given that efficacy data based on effort-dependent clinical outcome assessments and related endpoints have a high potential for bias. The FDA also requested additional information relating to Chemistry Manufacturing and Controls, or CMC, in the RTF letter. Dialogue with the FDA regarding the pegzilarginase BLA is ongoing.

In addition to our clinical programs, we have leveraged enzyme engineering to create additional pipeline candidates for the treatment of Cystinuria and other undisclosed diseases. These programs represent innovative solutions for diseases that previously were not believed to be addressable with enzyme therapies. For example, Cystinuria is a rare genetic disease characterized by frequent and recurrent kidney stone formation due to increased amounts of cystine in the urine. We engineered and optimized AGLE-325 to reduce plasma cystine and cysteine levels and therefore reduce urine cystine concentrations as an approach to inhibit cystine crystal and kidney stone formation. We announced in January 2023 that we are halting work on our preclinical pipeline candidates, including AGLE-325 for Cystinuria and that we will evaluate potential strategic options for these programs in order to maximize value.

We have incurred net losses in each year since inception. Our net losses were $83.8 million, $65.8 million, and $80.9 million for the years ended December 31, 2022, 2021, and 2020, 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, 2022, we had an accumulated deficit of $425.6 million. We expect to continue to incur operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and from year to year. We anticipate that our expenses will increase as we continue our clinical development activities for our product candidates, concurrently develop our pipeline product candidates, expand and protect our intellectual property portfolio, hire additional personnel, and continue to operate as a public company. Accordingly, based on recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our future operations, we determined that there is substantial doubt about our ability to continue as a going concern within twelve months of the issuance date of these financial statements.

**Business and Macroeconomic Conditions**

The extent of the impact of macroeconomic events and conditions, including inflation, increasing interest rates, increasing financial market volatility and uncertainty, the impact of war or military conflict, including the war in Ukraine and its potential supply chain impact, and public health pandemics, including the current COVID-19 pandemic and its variants, on our operational and financial performance will continue to depend on certain developments, including the impact on our clinical studies, employee or industry events, and effect on our suppliers and manufacturers, all of which are uncertain and cannot be predicted. Adverse effects of these large macroeconomic conditions have been prevalent in many of the areas where we, our CROs, suppliers or third-party business partners conduct business and as a result, we have experienced disruptions and may continue to experience more pronounced disruptions in our operations. With respect to our clinical trials, we have had patients miss scheduled dosings and experienced delays in enrollment due to the COVID-19 pandemic. We may continue to experience such delays as well as delays due to labor shortages and supply chain disruptions in distribution of clinical trial materials, study monitoring and data analysis that could materially adversely impact our business, results of operations and overall financial performance in future periods. As of the filing date of this Annual Report, the extent to which these macroeconomic events and conditions may impact our financial condition, results of operations or guidance is uncertain. The effect of these macroeconomic events and conditions may not be fully reflected in our results of operations and overall financial performance until future periods. See Part I, Item 1A “Risk Factors” for further discussion of the possible impact of these macroeconomic conditions, including inflation, increasing interest rates and the COVID-19 pandemic, on our business.

**Components of Operating Results**

***Revenue***

We have recognized license and development revenue from a license and supply agreement, or Immedica Agreement, with Immedica, and expect to continue to recognize revenue as we satisfy our performance obligations under the agreement. We may also be entitled to receive additional milestone payments pursuant to the Immedica Agreement upon achievement of specified milestones. As the recognition of future license and development revenue will be based on costs incurred to date relative to total estimated costs at completion and the uncertainty of when the events underlying various milestones are resolved, we expect our license and development revenue will fluctuate from period to period.

We have not generated any revenue from commercial product sales. Our ability to generate product revenues in the future will depend on the successful development, regulatory approval, and commercialization of our product candidates. In the future, we may also seek to generate revenue from a combination of research and development payments, license fees and other upfront or milestone payments, including under the Immedica Agreement.

***Research and development expenses***

Research and development expenses consist primarily of costs incurred for the discovery and development of our product candidates, including, pegtarviliase and pegzilarginase. We contract with external providers for nonclinical studies and clinical trials. Our research and development expenses include:

- costs from acquiring clinical trial materials and services performed for contracted services with contract manufacturing organizations, or CMOs;
- fees paid to clinical trial sites, clinical research organizations, or CROs, CMOs, nonclinical research companies, and academic institutions; and

- employee and consultant-related expenses incurred, which include salaries, benefits, travel and stock-based compensation.

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

Research and development expenses have historically represented the largest component of our total operating expenses.

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

- the scope, rate of progress, and expenses of our ongoing research activities as well as any additional clinical trials and other research and development activities;
- future clinical trial results;
- uncertainties in clinical trial enrollment rates or drop-out or discontinuation rates of patients;
- changes in the competitive drug development environment;
- potential safety monitoring or other studies requested by regulatory agencies;
- significant and changing government regulation;
- the timing and receipt of regulatory approvals, if any; and
- macroeconomic events and conditions, including inflation, increasing interest rates, increasing financial market volatility and uncertainty, the impact of war or military conflict, including the war in Ukraine and its potential supply chain impact, and public health pandemics, including the current COVID-19 pandemic.

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, legal, commercial development, operations, and human resources functions. Other significant costs include legal fees relating to corporate matters and fees for insurance, accounting, consulting, facilities, and recruiting services.

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

***Interest income***

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

***Income taxes***

We serve as a holding company for our ten wholly owned subsidiary corporations in the United States, United Kingdom, and European Union. We file a consolidated U.S. corporate federal income tax return with our eight United States subsidiaries. Additionally, we operate in the United Kingdom and our income tax return is subject to audit and adjustment

by local tax authorities. We use the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the financial statements and the tax bases of assets and liabilities. A valuation allowance is established against the deferred tax assets to reduce their carrying value to an amount that is more likely than not to be realized. The deferred tax assets and liabilities are classified as noncurrent along with the related valuation allowance. Due to our lack of earnings history, the net deferred tax assets have been fully offset by a valuation allowance.

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

**Critical Accounting Policies and Estimates**

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

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

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

***Revenue recognition***

We enter into license agreements related to our technologies that we have determined are within the scope of Accounting Standards Codification 606. Based on the terms and conditions of our agreements, we identify the goods and services that we promise to transfer to the customer, which may consist of the licensing of technologies, the performance of research and development activities, and/or the supply of products related to our technologies. Based on the nature of the goods and services provided and the customer's intended benefit of the arrangement, we evaluate which of the promised goods and services are distinct and, therefore, represent a performance obligation, which may require us to combine certain promised goods and services that are determined to not be distinct from one another. We also evaluate whether an agreement provides the customer an option to purchase future goods or services at a discounted price, or a material right, which would also represent a performance obligation.

In exchange for the performance obligations, we estimate the amount of consideration promised by the customer, or transaction price, which may include both fixed and variable consideration. Variable consideration, which may consist of various milestone payments based upon the achievement of certain events or conditions, sales-based royalties, or payments contingent on the performance of research and development services, are included in the transaction price only if we expect to receive such consideration and determine it is likely that the inclusion of the variable consideration will not result in a significant reversal in the cumulative amount of revenue recognized under the arrangement. Sales-based royalty and milestone payments that we determine are predominantly related to the license of our intellectual property are excluded from the transaction price we expect to receive until the underlying sales occur.

We allocate the estimated transaction price to the identified performance obligations based on the relative estimated stand-alone selling price, or SSP, of each performance. SSP is based on the observable price of our goods and services, or when SSP is not directly observable, we estimate SSP based on factors such as forecasted revenues or costs, development timelines, discount rates, probabilities of technical and regulatory success, and considerations such as market conditions and entity-specific factors. We recognize revenue allocated to each performance obligation either at a point-in-time or over time in a manner that depicts the transfer of control of the promised goods and services to the customer. For

performance obligations that are recognized over time, we estimate the measure of progress associated with the satisfaction of the performance obligation based on an input or output method, which may be based on factors such as costs incurred, labor hours expended, time elapsed, among other measures based on the nature of the performance obligation. The estimates made on an input or output method are subject to change and may result in material changes to revenue that could materially affect our results of operations. Please refer to Note 9, Strategic License Agreements, to the consolidated financial statements included 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 CROs and 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. However, there have been no material changes in estimates for the periods presented.

## Results of Operations

### Comparison of the Years Ended December 31, 2022 and 2021

A discussion and analysis of our financial condition and results of operations for the year ended December 31, 2020 is included in Item 7 of Part II, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2021 filed with the SEC on March 8, 2022.

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021, together with the changes in those items in dollars and as a percentage:

| | Year Ended December 31, | | Dollar Change | % Change |
|---|---|---|---|---|
| | 2022 | 2021 | | |
| | | (in thousands) | | |
| Revenue: | | | | |
| License | $ — | $ 12,000 | $ (12,000) | * |
| Development fee | 2,329 | 6,739 | (4,410) | -65% |
| Total revenue | 2,329 | 18,739 | (16,410) | -88% |
| | | | | |
| Operating expenses: | | | | |
| Research and development | 58,579 | 57,069 | 1,510 | 3% |
| General and administrative | 28,531 | 27,319 | 1,212 | 4% |
| Total operating expenses | 87,110 | 84,388 | 2,722 | 3% |
| Loss from operations | (84,781) | (65,649) | (19,132) | 29% |
| Interest income | 837 | 111 | 726 | * |
| Other expense, net | (7) | (122) | 115 | -94% |
| Loss before income tax expense | (83,951) | (65,660) | (18,291) | 28% |
| Income tax benefit (expense) | 136 | (141) | 277 | -196% |
| Net loss | $ (83,815) | $ (65,801) | $ (18,014) | 27% |

* Percentage not meaningful

*License and Development Fee Revenue.* For the year ended December 31, 2022, we recognized $2.3 million of development fee revenue allocated to the PEACE Phase 3 trial and BLA package of the Immedica Agreement. For the year ended December 31, 2021, we recognized $18.7 million of license and development fee revenue in connection with the Immedica Agreement. The total revenue generated was attributable to $12.0 million allocated to the license and $6.7 million allocated to the PEACE Phase 3 trial and BLA package. Please refer to Note 9, Strategic License Agreements, to the consolidated financial statements included elsewhere in this Annual Report for additional disclosures around revenue recognition.

*Research and Development Expenses*. Research and development expenses increased $1.5 million, or 3%, to $58.6 million for the year ended December 31, 2022 from $57.1 million for the year ended December 31, 2021. The change in research and development expenses was due to:

- a $1.1 million increase in expenses associated with pegzilarginase primarily due to a $1.4 million increase related to activities involved in closing the PEACE trial and ramping up the new open-label extension trial for the treatment of patients with Arginase 1 Deficiency, partially offset by a $0.3 million decrease in professional services to support the pegzilarginase program;
- a $2.8 million increase in expense associated with IND-enabling activities of AGLE-325 for the treatment of patients with Cystinuria;
- a $0.6 million increase in personnel-related expenses, primarily driven by an increase of headcount expenses;
- a $1.5 million decrease in expenses primarily associated with the completion of non-clinical toxicology studies in the prior year for pegtarviliase for the treatment of patients with Homocystinuria;
- a $0.6 million decrease due to reduction in preclinical lab work; and
- a $0.9 million decrease in other research and development expenses, primarily related to a reduction of consulting and recruiting activities.

*General and Administrative Expenses*. General and administrative expenses increased by $1.2 million, or 4%, to $28.5 million for the year ended December 31, 2022 from $27.3 million for the year ended December 31, 2021. The increase in general and administrative expenses was primarily due to a $0.8 million increase in expense related to our commercial capabilities and infrastructure and $0.4 million increase in expenses related to financing activities.

## Liquidity and Capital Resources

### *Sources of liquidity*

We are a clinical-stage biotechnology company with a limited operating history, and due to our significant research and development expenditures, we have generated operating losses since our inception and have not generated any revenue from the sale of any products. Since our inception and through December 31, 2022, we have funded our operations primarily by raising an aggregate of $506.2 million of gross proceeds from the sale and issuance of convertible preferred and common equity securities, pre-funded stock warrants, the collection of grant proceeds, and the licensing of our product rights for the commercialization of pegzilarginase in Europe and several countries in the Middle East.

In March 2021, we entered into the Immedica Agreement, pursuant to which Immedica licensed the product rights for commercialization of pegzilarginase in the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman. In April 2021, we received an upfront payment of $21.5 million from Immedica. Under the terms of the Immedica Agreement, we are also eligible to receive additional payments of up to approximately $120.8 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.07 to €1.00. Additionally, we are entitled to receive royalties in the mid-20 percent range on the net sales of the product in countries included in the Immedica Agreement. In July 2021, the Immedica Agreement was modified to include additional development services, up to $3.0 million, to support the PEACE Phase 3 trial and BLA package performance obligation.

During the year ended December 31, 2020, we raised $163.3 million of gross proceeds through an underwritten public offering and an at-the-market offering program. We sold 15,442,303 shares of common stock and pre-funded warrants to purchase up to 13,610,328 shares of common stock in an underwritten public offering, or the 2020 Public Offering, for gross proceeds of $138.0 million, resulting in net proceeds of $129.0 million after deducting underwriting discounts, commissions, and offering costs. Additionally, we sold an aggregate of 3,245,077 shares of common stock under an at-the-market offering program, or the 2020 ATM, for gross proceeds of $25.3 million, resulting in net proceeds of $24.6 million, after deducting underwriting discounts, commissions, and offering costs.

The shares of common stock and pre-funded warrants sold in the 2020 Public Offering were pursuant to a shelf registration statement on Form S-3, declared effective in February 2019 by the SEC for the potential offering, issuance and sale by us of up to $200.0 million of our common stock, warrants to purchase common stock, and other security types and subscription rights. The shares of common stock sold under the 2020 ATM were pursuant to an April 2020 sales agreement with JonesTrading Institutional Services LLC, as sales agent, to issue and sell shares of our common stock for an aggregate offering price of $60.0 million. In February 2022, the shelf registration statement the 2020 ATM was registered under expired and no sales under this registration statement will occur going forward.

In July 2020, we filed a shelf registration statement on Form S-3, or the 2020 Registration Statement, that was declared effective by the SEC for the potential offering, issuance and sale by us of up to $400.0 million of our common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock and debt securities, subscription rights to purchase common stock and units consisting of all or some of these securities.

In May 2022, we sold 10,752,688 shares of common stock and pre-funded warrants to purchase up to 17,372,312 shares of common stock in a registered direct offering, or the 2022 RDO, for gross proceeds of $45.0 million, resulting in net proceeds of $42.9 million after deducting placement agent fees and offering costs. The shares of common stock and pre-funded warrants sold in the 2022 RDO were offered pursuant to the 2020 Registration Statement.

Also in May 2022, we entered into a sales agreement, or the 2022 Sales Agreement, with JonesTrading Institutional Services LLC, as sales agent, to issue and sell shares of our common stock for an aggregate offering price of $60.0 million under an at-the-market offering program with JonesTrading Institutional Services LLC, pursuant to the 2020 Registration Statement. As of the date of the filing of this report, $60.0 million of our common stock remained available for sale pursuant to the 2022 Sales Agreement. Any sales of common stock to be sold under the 2022 Sales Agreement will be made pursuant to the 2020 Registration Statement.

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

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

Our operational plan for the near future is to continue clinical trials for our product candidate pegtarviliase in Classical Homocystinuria and our product candidate pegzilarginase in Arginase 1 Deficiency. As such, we plan to focus our research and development expenditures and general and administrative expenditures on nonclinical studies, clinical trials, manufacturing, and commercial development. We expect our principal expenditures during this time period to include expenses for the following:

- funding the continuing development of pegtarviliase and pegzilarginase; and
- funding working capital, including general operating expenses.

Due to our significant research and development expenditures, we have generated substantial losses in each period since inception. We have an accumulated deficit of $425.6 million as of December 31, 2022. We anticipate that we will continue to generate losses into the foreseeable future as we develop our product candidates, seek regulatory approval of those candidates and begin to commercialize any approved products. Until such time as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity or debt financings, collaborations, license and development agreements, or other sources. We currently have no debt, credit facility or additional committed capital. To the extent that we raise additional equity, the ownership interest of our stockholders will be diluted.

Based on our available cash, cash equivalents, marketable securities, and restricted cash of $57.3 million as of December 31, 2022, we believe that we have sufficient resources to fund our operations into the fourth quarter of 2023. Accordingly, based on recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance our future operations, we determined that there is substantial doubt about our ability to continue as a going concern within one year after the date that the financial statements included in this Annual Report filed on Form 10-K are issued. As a result, in order to continue to operate our business beyond that time, we will need to raise additional funds. However, there can be no assurance that we will be able to generate funds on terms acceptable to us, on a timely basis, or at all. In addition, we have based this estimate on assumptions that may prove to be wrong, and we could deplete our capital resources sooner than we currently anticipate.

***Cash flows***

A discussion and analysis of our financial condition and cash flows for the year ended December 31, 2020 is included in Item 7 of Part II, “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2021 filed with the SEC on March 8, 2022.

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

| | Year Ended December 31, | |
|---|---|---|
| | 2022 | 2021 |
| Net cash and cash equivalents (used in) provided by: | | |
| Operating activities | $ (80,144) | $ (53,716) |
| Investing activities | 57,008 | (22,619) |
| Financing activities | 42,678 | 1,393 |
| Effect of exchange rate on cash, cash equivalents, and restricted cash | (106) | (15) |
| Net increase (decrease) in cash and cash equivalents | $ 19,436 | $ (74,957) |

*Cash used in operating activities*

Cash used in operating activities for the year ended December 31, 2022 was $80.1 million and reflected a net loss of $83.8 million. The cash impact of our net loss was offset by non-cash expenses of $7.1 million for stock-based compensation, $1.6 million for depreciation and amortization, $0.4 million for operating lease expense, and $0.1 million for net premium purchase and amortization on marketable securities. The net decrease in operating assets and liabilities of $5.5 million was primarily related to a $2.6 million decrease in accounts payable, a $1.1 million increase in prepaid expenses and other assets, a $0.9 million decrease in deferred revenue due to receiving payments under the Immedica Agreement offset by the recognition of revenue allocated to the license, PEACE Phase 3 trial and BLA filing, a $0.9 million decrease in accrued expenses and other liabilities, and a $0.4 million decrease in operating lease liabilities due to lease payments made during the year, partially offset by a $0.4 million increase in accounts receivable for incremental services provided to Immedica and not yet paid.

Cash used in operating activities for the year ended December 31, 2021 was $53.7 million and reflected a net loss of $65.8 million. The cash impact of our net loss was offset by non-cash expenses of $8.0 million for stock-based compensation, $1.6 million for depreciation and amortization, $0.4 million for operating lease expense, and $0.2 million for net premium purchase and amortization on marketable securities. The net change in operating assets and liabilities of $1.8 million was primarily related to a $3.6 million increase in deferred revenue due to receiving a $21.5 million upfront payment under the Immedica Agreement offset by the recognition of revenue allocated to the license, PEACE Phase 3 trial and BLA submission. Additional offsets included a $1.2 million increase in prepaid expenses and other assets due to advance payments for the Phase 1/2 trial of pegtarviliase and manufacturing activities for the Arginase 1 Deficiency program, a $0.8 million increase in license and development receivable for incremental services provided to Immedica and not yet paid, and a $0.4 million decrease in operating lease liabilities due to lease payments made during the year.

*Cash used in investing activities*

Cash used in investing activities for the year ended December 31, 2022 was $57.0 million and consisted of $39.5 million in purchases of marketable securities offset by $96.5 million in maturities of marketable securities.

Cash used in investing activities for the year ended December 31, 2021 was $22.6 million and consisted of $133.1 million in purchases of marketable securities and $0.5 million in purchases of property and equipment offset by $111.0 million in maturities of marketable securities.

*Cash provided by financing activities*

Cash provided by financing activities for the year ended December 31, 2022 was $42.7 million, which consisted of $42.9 million from issuance of common stock and pre-funded warrants in a registered direct offering, the 2022 RDO, net of offering costs and $0.2 million sale of common stock under our 2016 Employee Stock Purchase Plan offset by $0.4 million in principal payments made on finance lease obligations.

Cash provided by financing activities for the year ended December 31, 2021 was $1.4 million, which consisted of $1.9 million in stock option exercises and sale of common stock under our 2016 Employee Stock Purchase Plan offset by $0.5 million in principal payments made on finance lease obligations.

**Contractual Obligations and Other Commitments**

In April 2019, we entered into a lease agreement, or the Las Cimas Lease, for our corporate headquarters and laboratory space located in Austin, Texas. Future minimum lease commitments under the Las Cimas Lease through April 2028 are $6.1 million. Please refer to Note 7, Leases, to the consolidated financial statements included elsewhere in this Annual Report for additional disclosures.

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

***Contingent contractual obligations***

In June 2015, we entered into a Cancer Research Grant Contract, or the Grant Contract, with the Cancer Prevention and Research Institute of Texas, or CPRIT, under which CPRIT awarded us a grant not to exceed $19.8 million to be used

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

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, or the University, for certain intellectual property owned by the University related to our program candidates for cystinase and methioninase. In January 2017, we and the University entered into an Amended and Restated Patent License Agreement, or the Restated License, which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us. The Restated License was amended in August 2017, December 2017, and December 2018 to revise diligence milestones and license additional patent applications, including our program candidates under our pegtarviliase and Cystinuria programs.

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

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

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

As of December 31, 2022, we held $57.3 million in cash, cash equivalents, marketable securities, and restricted cash, all of which was denominated in U.S. dollar assets, and consisting primarily of investments in money market funds, commercial paper, and corporate bonds.

We are also exposed to market risk related to changes in foreign currency exchange rates, as a result of entering into transactions denominated in currencies other than U.S. dollars. Due to the uncertain timing of expected payments in foreign currencies, we do not utilize any forward exchange contracts. All foreign transactions settle on the applicable spot exchange basis at the time such payments are made. For the year ended December 31, 2022, a majority of our expenditures were denominated in U.S. dollars. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

## ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

### AEGLEA BIOTHERAPEUTICS, INC.

### INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

## Report of Independent Registered Public Accounting Firm

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

### *Opinion on the Financial Statements*

We have audited the accompanying consolidated balance sheets of Aeglea BioTherapeutics, Inc. and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations, of comprehensive loss, of changes in stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2022, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 in conformity with accounting principles generally accepted in the United States of America.

*Substantial Doubt About the Company's Ability to Continue as a Going Concern*

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company has not generated any product revenues and has not achieved profitable operations. These conditions raise substantial doubt about the Company's ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

### *Basis for Opinion*

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

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

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

### *Critical Audit Matters*

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

*Accrued Contracted Research and Development Costs*

As described in Notes 2 and 6 to the consolidated financial statements, the Company has entered into various agreements with contract research organizations (CROs), contract manufacturing organizations (CMOs), and other outside service providers. Management records 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. The Company's research and development expense for the year ended December 31, 2022 was $59 million, a portion of which relates to contracted research and development costs. Within accrued and other current liabilities, management has accrued $7 million of contracted research and development costs as of December 31, 2022.

The principal consideration for our determination that performing procedures relating to accrued contracted research and development costs is a critical audit matter is a high degree of auditor effort in performing procedures related to management's estimate of the accrued contracted research and development costs.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures also included, among others (i) testing management's process for estimating accrued contracted research and development costs, (ii) testing the completeness and accuracy of the data used to develop the estimate, (iii) testing the completeness and accuracy of costs incurred, on a sample basis, by tracing information to the underlying contracts, purchase orders, invoices and information received from certain third party service providers, where applicable, and (iv) evaluating the reasonableness of the estimated costs incurred for the services which have not been invoiced by tracing to underlying supporting documentation, such as underlying contracts, purchase orders and information received from certain third party service, providers, where applicable.

/s/ PricewaterhouseCoopers LLP
Austin, Texas
March 2, 2023

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

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

**(In thousands, except share and per share amounts)**

| | December 31, 2022 | December 31, 2021 |
|---|---|---|
| **ASSETS** | | |
| CURRENT ASSETS | | |
| Cash and cash equivalents | $ 34,863 | $ 15,142 |
| Marketable securities | 20,848 | 77,986 |
| Development receivable | 375 | 815 |
| Prepaid expenses and other current assets | 6,172 | 4,948 |
| Total current assets | 62,258 | 98,891 |
| Restricted cash | 1,553 | 1,838 |
| Property and equipment, net | 3,220 | 4,549 |
| Operating lease right-of-use assets | 3,430 | 3,806 |
| Other non-current assets | 683 | 842 |
| TOTAL ASSETS | $ 71,144 | $ 109,926 |
| | | |
| **LIABILITIES AND STOCKHOLDERS' EQUITY** | | |
| CURRENT LIABILITIES | | |
| Accounts payable | $ 677 | $ 3,319 |
| Operating lease liabilities | 625 | 436 |
| Deferred revenue | 517 | 2,359 |
| Accrued and other current liabilities | 12,837 | 14,030 |
| Total current liabilities | 14,656 | 20,144 |
| Non-current operating lease liabilities | 4,004 | 4,608 |
| Deferred revenue, net of current portion | 2,179 | 1,217 |
| Other non-current liabilities | — | 16 |
| TOTAL LIABILITIES | 20,839 | 25,985 |
| Commitments and Contingencies (Note 9) | | |
| | | |
| STOCKHOLDERS' EQUITY | | |
| Preferred stock, $0.0001 par value; 10,000,000 shares authorized as of December 31, 2022 and 2021; no shares issued and outstanding as of December 31, 2022 and 2021 | — | — |
| Common stock, $0.0001 par value; 500,000,000 shares authorized as of December 31, 2022 and 2021, 65,350,343 shares and 49,355,130 shares issued and outstanding as of December 31, 2022 and 2021, respectively | 6 | 5 |
| Additional paid-in capital | 475,971 | 425,765 |
| Accumulated other comprehensive (loss) income | (48) | (20) |
| Accumulated deficit | (425,624) | (341,809) |
| TOTAL STOCKHOLDERS' EQUITY | 50,305 | 83,941 |
| TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY | $ 71,144 | $ 109,926 |

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, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| Revenue: | | | |
| License | $ — | $ 12,000 | $ — |
| Development fee | 2,329 | 6,739 | — |
| Total revenue | 2,329 | 18,739 | — |
| | | | |
| Operating expenses: | | | |
| Research and development | 58,579 | 57,069 | 59,638 |
| General and administrative | 28,531 | 27,319 | 21,843 |
| Total operating expenses | 87,110 | 84,388 | 81,481 |
| Loss from operations | (84,781) | (65,649) | (81,481) |
| | | | |
| Other income (expense): | | | |
| Interest income | 837 | 111 | 593 |
| Other expense, net | (7) | (122) | (5) |
| Total other income (expense) | 830 | (11) | 588 |
| Loss before income tax expense | (83,951) | (65,660) | (80,893) |
| Income tax benefit (expense) | 136 | (141) | — |
| Net loss | $ (83,815) | $ (65,801) | $ (80,893) |
| | | | |
| Net loss per share, basic and diluted | $ (0.99) | $ (1.00) | $ (1.52) |
| Weighted-average common shares outstanding, basic and diluted | 84,280,785 | 65,744,611 | 53,371,730 |

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, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| Net loss | $ (83,815) | $ (65,801) | $ (80,893) |
| Other comprehensive income (loss): | | | |
| Foreign currency translation adjustment | (35) | (1) | 19 |
| Unrealized gain (loss) on marketable securities | 7 | (30) | (59) |
| Total comprehensive loss | $ (83,843) | $ (65,832) | $ (80,933) |

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

**Aeglea BioTherapeutics, Inc.**
**Consolidated Statements of Changes in Stockholders' Equity**
**(In thousands)**

| | Common Stock | | Additional Paid-in Capital | Accumulated Other Comprehensive (Loss) Income | Accumulated Deficit | Total Stockholders' Equity |
|---|---|---|---|---|---|---|
| | Shares | Amount | | | | |
| Balances—December 31, 2019 | 29,084 | $ 3 | $ 255,142 | $ 51 | $ (195,115) | $ 60,081 |
| Issuance of common stock and pre-funded warrants in connection with public and at-the-market offerings, net of offering costs | 18,688 | 2 | 153,570 | — | — | 153,572 |
| Issuance of common stock in connection with exercise of stock options | 127 | — | 490 | — | — | 490 |
| Issuance of common stock in connection with employee stock purchase plan | 60 | — | 366 | — | — | 366 |
| Stock-based compensation expense | — | — | 6,256 | — | — | 6,256 |
| Foreign currency translation adjustment | — | — | — | 19 | — | 19 |
| Unrealized loss on marketable securities | — | — | — | (59) | — | (59) |
| Net loss | — | — | — | — | (80,893) | (80,893) |
| Balances—December 31, 2020 | 47,959 | $ 5 | $ 415,824 | $ 11 | $ (276,008) | $ 139,832 |
| Issuance of common stock in connection with exercise of pre-funded warrants | 1,000 | — | — | — | — | — |
| Issuance of common stock in connection with exercise of stock options | 313 | — | 1,449 | — | — | 1,449 |
| Issuance of common stock in connection with employee stock purchase plan | 83 | — | 454 | — | — | 454 |
| Stock-based compensation expense | — | — | 8,038 | — | — | 8,038 |
| Foreign currency translation adjustment | — | — | — | (1) | — | (1) |
| Unrealized loss on marketable securities | — | — | — | (30) | — | (30) |
| Net loss | — | — | — | — | (65,801) | (65,801) |
| Balances—December 31, 2021 | 49,355 | $ 5 | $ 425,765 | $ (20) | $ (341,809) | $ 83,941 |
| Issuance of common stock and pre-funded warrants in connection with registered direct offering, net of offering costs | 10,753 | 1 | 42,873 | — | — | 42,874 |
| Issuance of common stock in connection with exercise of pre-funded warrants | 5,090 | — | — | — | — | — |
| Issuance of common stock in connection with employee stock purchase plan | 152 | — | 222 | — | — | 222 |
| Stock-based compensation expense | — | — | 7,111 | — | — | 7,111 |
| Foreign currency translation adjustment | — | — | — | (35) | — | (35) |
| Unrealized gain (loss) on marketable securities | — | — | — | 7 | — | 7 |
| Net loss | — | — | — | — | (83,815) | (83,815) |
| Balances—December 31, 2022 | 65,350 | $ 6 | $ 475,971 | $ (48) | $ (425,624) | $ 50,305 |

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, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| **CASH FLOWS FROM OPERATING ACTIVITIES** | | | |
| Net loss | $ (83,815) | $ (65,801) | $ (80,893) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | |
| Stock-based compensation | 7,111 | 8,038 | 6,256 |
| Depreciation and amortization | 1,567 | 1,576 | 996 |
| Purchase net (premium) discount on marketable securities | 428 | (344) | (286) |
| Net amortization of premium (accretion of discount) on marketable securities | (327) | 548 | 73 |
| Non-cash operating lease expense | 397 | 425 | 628 |
| Other | (2) | 9 | (9) |
| Changes in operating assets and liabilities: | | | |
| Development receivable | 440 | (815) | — |
| Accounts payable | (2,641) | 1,065 | (544) |
| Prepaid expenses and other assets | (1,144) | (1,216) | (1,101) |
| Deferred revenue | (880) | 3,576 | — |
| Operating lease liabilities | (435) | (404) | 251 |
| Accrued and other liabilities | (843) | (373) | (1,146) |
| Net cash used in operating activities | (80,144) | (53,716) | (75,775) |
| **CASH FLOWS FROM INVESTING ACTIVITIES** | | | |
| Purchases of property and equipment | (38) | (573) | (4,280) |
| Purchases of marketable securities | (39,500) | (133,079) | (129,000) |
| Proceeds from maturities and sales of marketable securities | 96,546 | 111,033 | 125,676 |
| Net cash provided by (used in) investing activities | 57,008 | (22,619) | (7,604) |
| **CASH FLOWS FROM FINANCING ACTIVITIES** | | | |
| Proceeds from issuance of common stock and pre-funded warrants in registered direct offering, net of offering costs | 42,874 | — | 153,716 |
| Proceeds from employee stock plan purchases and stock option exercises | 222 | 1,903 | 816 |
| Principal payments on finance lease obligation | (418) | (510) | (20) |
| Net cash provided by financing activities | 42,678 | 1,393 | 154,512 |
| Effect of exchange rate on cash, cash equivalents, and restricted cash | (106) | (15) | 51 |
| NET (DECREASE) INCREASE IN CASH, CASH EQUIVALENTS, AND RESTRICTED CASH | 19,436 | (74,957) | 71,184 |
| **CASH, CASH EQUIVALENTS, AND RESTRICTED CASH** | | | |
| Beginning of period | 16,980 | 91,937 | 20,753 |
| End of period | $ 36,416 | $ 16,980 | $ 91,937 |
| **Supplemental Disclosure of Non-Cash Investing and Financing Information:** | | | |
| Leased assets obtained in exchange for lease obligations | $ 21 | $ 872 | $ 172 |
| Unpaid amounts related to purchase of property and equipment | $ — | $ — | $ 224 |

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

## 1. The Company and Basis of Presentation

Aeglea BioTherapeutics, Inc. ("Aeglea" or the "Company") is a clinical-stage biotechnology company developing human enzyme therapeutics to benefit people with rare metabolic diseases. The Company was formed as a Limited Liability Company (LLC) in Delaware on December 16, 2013 under the name Aeglea BioTherapeutics Holdings, LLC and was converted from a Delaware LLC to a Delaware corporation on March 10, 2015. The Company operates in one segment and has its principal offices in Austin, Texas.

### *Liquidity*

As of December 31, 2022, the Company had working capital of $47.6 million, an accumulated deficit of $425.6 million, and cash, cash equivalents, marketable securities, and restricted cash of $57.3 million. The Company has not generated any product revenues and has not achieved profitable operations. There is no assurance that profitable operations will ever be achieved, and, if achieved, could be sustained on a continuing basis. In addition, development activities, clinical and nonclinical testing, and commercialization of the Company's products will require significant additional financing.

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

In accordance with ASC 205-40, Going Concern, the Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date the financial statements included in this Annual Report on Form 10-K are issued. Based upon the Company's current operating plans, the Company believes that it has sufficient resources to fund operations into the fourth quarter of 2023 with its existing cash, cash equivalents, and marketable securities. Accordingly, based on its recurring losses from operations incurred since inception, the expectation of continued operating losses, and the need to raise additional capital to finance its future operations, the Company determined that there is substantial doubt about the Company's ability to continue as a going concern within twelve months of the issuance date of these financial statements. The accompanying consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty and assumes the Company will continue as a going concern through the realization of assets and satisfaction of liabilities and commitments in the ordinary course of business. The Company plans to address this condition through the sale of common stock in public offerings and/or private placements, debt financings, or through other capital sources, including collaborations with other companies or other strategic transactions.

Although the Company has been successful in raising capital in the past, there is no assurance that it will be successful in obtaining such additional financing on terms acceptable to the Company, if at all, nor is it considered probable under the accounting standards. If the Company is unable to obtain sufficient funding on acceptable terms, it could be forced to delay, reduce or eliminate some or all of its research and development programs or commercialization activities, which could materially adversely affect its business prospects or its ability to continue operations.

### *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. 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, the results of which form the basis for making

judgements about the carrying value of assets, liabilities, and equity and the amount of revenues and expenses. Estimates are used in accounting for, among other items, accrued research and development costs and revenue recognition. Actual results could differ materially from those estimates.

***Cash and Cash Equivalents***

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

***Marketable Securities***

All investments have been classified as available-for-sale and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its investments in debt securities at the time of purchase. The Company may hold securities with stated maturities greater than one year until maturity. All available-for-sale securities are considered available to support current operations and are classified as current assets. The Company presents credit losses as an allowance rather than as a reduction in the amortized cost of the available-for-sale securities.

For available-for-sale debt securities in an unrealized loss position, the Company first assesses whether it intends to sell, or it is more likely than not that it will be required to sell the security before recovery of its amortized cost basis. If either of the criteria regarding intent or requirement to sell is met, the security's amortized cost basis is written down to fair value and recognized in other income (expense) in the results of operations. For available-for-sale debt securities that do not meet the aforementioned criteria, the Company evaluates whether the decline in fair value has resulted from credit losses or other factors. In making this assessment, management considers the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency, and adverse conditions specifically related to the security, among other factors. If this assessment indicates that a credit loss exists, an allowance is recorded for the difference between the present value of cash flows expected to be collected and the amortized cost basis of the security. Impairment losses attributable to credit loss factors are charged against the allowance when management believes an available-for-sale security is uncollectible or when either of the criteria regarding intent or requirement to sell is met.

Any unrealized losses from declines in fair value below the amortized cost basis as a result of non-credit loss factors is recognized as a component of accumulated other comprehensive (loss) income, along with unrealized gains. Realized gains and losses and declines in fair value, if any, on available-for-sale securities are included in other income (expense) in the results of operations. The cost of securities sold is based on the specific-identification method.

***Restricted Cash***

Restricted cash consists of money market accounts held by financial institutions as collateral for the Company's obligations under a credit agreement and a facility lease for the Company's corporate headquarters in Austin, Texas.

***Concentration of Credit Risk***

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

***Property and Equipment***

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

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

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

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

Long-lived assets are reviewed for indications of possible impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability is measured by comparison of the carrying amounts to the future undiscounted cash flows attributable to these assets. An impairment loss is recognized to the extent an asset group is not recoverable, and the carrying amount exceeds the fair value. There were no impairments of long-lived assets for the years ended December 31, 2022, 2021, and 2020.

***Accrued Research and Development Costs***

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

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

***Leases***

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

The Company has lease agreements with lease and non-lease components. As allowed under Topic 842, the Company has elected to not separate lease and non-lease components for any leases involving real estate and office equipment classes of assets and, as a result, accounts for the lease and non-lease components as a single lease

component. The Company has also elected to not apply the recognition requirement of Topic 842 to leases with a term of 12 months or less for all classes of assets.

***Fair Value of Financial Instruments***

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

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

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

Level 1: Observable inputs, such as quoted prices in active markets for identical assets or liabilities.

Level 2: Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3: Valuations based on unobservable inputs to the valuation methodology and including data about assumptions that market participants would use in pricing the asset or liability based on the best information available under the circumstances.

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

***Revenue Recognition***

Under ASC Topic 606, "Revenue from Contracts with Customers" ("Topic 606"), an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation.

The Company assesses its license arrangements within the scope of Topic 606 in accordance with this framework as follows:

*License revenue*

The Company assesses whether the goods or services promised within each contract are distinct to identify those that are performance obligations. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. In assessing whether a promised good or service is distinct, and therefore a performance obligation, the Company considers factors such as the research, stage of development of the licensed product, manufacturing and commercialization capabilities of the customer and the availability of the associated expertise in the general marketplace. The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, the Company is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct. Arrangements that include rights to additional goods or services that are exercisable at a customer's

discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered performance obligations.

The transaction price is determined and allocated to the identified performance obligations in proportion to their stand-alone selling prices ("SSP") on a relative SSP basis. SSP is based on observable prices of the performance obligations or, when such prices are not observable, are estimated. The estimation of SSP may include factors such as forecasted revenues or costs, development timelines, discount rates, probabilities of technical and regulatory success, and considerations such as market conditions and entity-specific factors. In certain circumstances, the Company may apply the residual method to determine the SSP of a good or service if the SSP is considered highly variable or uncertain. The Company validates the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the amount of estimated variable consideration in the transaction price to the extent that it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development, regulatory or commercial milestone payments, the Company evaluates whether the milestones are considered likely of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant cumulative revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are generally not considered likely of being achieved until those approvals are received.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensee and the transfer of the promised goods or services to the licensees will be one year or less. For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and if the license is deemed to be the predominant item to which the royalties relate, the Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

The Company recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time, recognition is based on the use of an output or input method.

The Company's contracts may be modified for changes in the customer's requirements. If contract modifications are for additional goods and services that are distinct from the existing contract, the modification will be accounted for as either a separate contract or a termination of the existing contract, depending on whether the additional goods or services reflects the SSP.

If the additional goods or services in a contract modification are not distinct from the existing contract, they are accounted for as if they were part of the original contract. The effect of the contract modification on the transaction price and the measure of progress for the performance obligation to which it relates is recognized as an adjustment to revenue on a cumulative catch-up basis. The cumulative catch-up adjustment is calculated using an updated measure of progress applied to the sum of (1) the remaining consideration allocated to the partially satisfied performance obligation and (2) the revenue already recognized on that performance obligation. The revenue recognized for fully satisfied goods or services and distinct from the remaining performance obligations is not altered by the modification.

*Collaborative arrangements*

The Company analyzes its license arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, Collaborative

Arrangements (“Topic 808”). This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For arrangements within the scope of Topic 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of Topic 808 and which elements of the collaboration are more reflective of a vendor-customer relationship and therefore within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to Topic 808, an appropriate recognition method is determined and applied consistently, either by analogy to authoritative accounting literature or by applying a reasonable and rational policy election. For those elements of the arrangement that are accounted for pursuant to Topic 606, the Company applies the five-step model described above.

***Research and Development Costs***

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

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

***Stock-Based Compensation***

The Company recognizes the cost of stock-based awards granted to employees and non-employees based on the estimated grant-date fair values of the awards. The fair values of stock options are estimated on the date of grant using the Black-Scholes option pricing model. The fair values of restricted stock units (“RSUs”) are based on the fair value of the Company’s common stock on the date of the grant. The value of the award is recognized as compensation expense on a straight-line basis over the requisite service period. Forfeitures are recognized when they occur, which may result in the reversal of compensation costs in subsequent periods as the forfeitures arise. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable.

***Income Taxes***

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

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

The Company recognizes benefits of uncertain tax positions if it is more likely than not that such positions will be sustained upon examination based solely on the technical merits, as the largest amount of benefits that is more likely than not to be realized upon the ultimate settlement. The Company’s policy is to recognize interest and penalties related to the unrecognized tax benefits as a component of income tax expense, if applicable. As of December 31, 2022 and 2021, the Company had no unrecognized tax benefits and there were no interest or penalties incurred by the Company in the years ended December 31, 2022, 2021, or 2020.

***Comprehensive Loss***

Comprehensive loss is the change in stockholders’ equity from transactions and other events and circumstances other than those resulting from investments by stockholders and distributions to stockholders. The Company’s other comprehensive income (loss) is currently comprised of changes in unrealized losses and gains on available-for-sale securities and foreign currency translation adjustments reflecting the cumulative effect of changes in exchange rates between the foreign entity’s functional currency and the reporting currency.

## 3. Fair Value Measurements

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

| | December 31, 2022 | | | |
|---|---|---|---|---|
| | Level 1 | Level 2 | Level 3 | Total |
| Financial Assets | | | | |
| Money market funds | $ 15,250 | $ — | $ — | $ 15,250 |
| Commercial paper | — | 23,641 | — | 23,641 |
| U.S. government securities | — | 4,230 | — | 4,230 |
| Corporate bonds | — | 3,732 | — | 3,732 |
| Total financial assets | $ 15,250 | $ 31,603 | $ — | $ 46,853 |

| | December 31, 2021 | | | |
|---|---|---|---|---|
| | Level 1 | Level 2 | Level 3 | Total |
| Financial Assets | | | | |
| Money market funds | $ 8,888 | $ — | $ — | $ 8,888 |
| Commercial paper | — | 65,412 | — | 65,412 |
| Corporate bonds | — | 12,574 | — | 12,574 |
| Total financial assets | $ 8,888 | $ 77,986 | $ — | $ 86,874 |

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 U.S. government agency securities, commercial paper and corporate bonds, and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data.

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

## 4. Cash Equivalents and Marketable Securities

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

| | December 31, 2022 | | | |
|---|---|---|---|---|
| | Amortized Cost | Gross Unrealized Gains | Gross Unrealized Losses | Estimated Fair Value |
| Cash equivalents: | | | | |
| Money market funds | $ 15,250 | $ — | $ — | $ 15,250 |
| Commercial paper | 7,021 | 1 | (2) | 7,020 |
| U.S. government securities | 3,736 | — | (1) | 3,735 |
| Total cash equivalents | 26,007 | 1 | (3) | 26,005 |
| | | | | |
| Marketable securities: | | | | |
| Commercial paper | 16,644 | 2 | (25) | 16,621 |
| Corporate bonds | 3,738 | — | (6) | 3,732 |
| U.S. government securities | 495 | — | — | 495 |
| Total marketable securities | $ 20,877 | $ 2 | $ (31) | $ 20,848 |

| | December 31, 2021 | | | |
|---|---|---|---|---|
| | Amortized Cost | Gross Unrealized Gains | Gross Unrealized Losses | Estimated Fair Value |
| Cash equivalents: | | | | |
| Money market funds | $ 8,888 | $ — | $ — | $ 8,888 |
| Total cash equivalents | 8,888 | — | — | 8,888 |
| | | | | |
| Marketable securities: | | | | |
| Commercial paper | 65,443 | 3 | (34) | 65,412 |
| Corporate bonds | 12,581 | — | (7) | 12,574 |
| Total marketable securities | $ 78,024 | $ 3 | $ (41) | $ 77,986 |

The following table summarizes the available-for-sale securities in an unrealized loss position for which an allowance for credit losses has not been recorded as of December 31, 2022 and 2021, aggregated by major security type and length of time in a continuous unrealized loss position:

| | December 31, 2022 | | | | | |
|---|---|---|---|---|---|---|
| | Less Than 12 Months | | 12 Months or Longer | | Total | |
| | Fair Value | Unrealized Losses | Fair Value | Unrealized Losses | Fair Value | Unrealized Losses |
| Commercial paper | $ 17,699 | $ (27) | $ — | $ — | $ 17,699 | $ (27) |
| U.S. government securities | 3,735 | (1) | — | — | 3,735 | (1) |
| Corporate bonds | 3,732 | (6) | — | — | 3,732 | (6) |
| Total marketable securities | $ 25,166 | $ (34) | $ — | $ — | $ 25,166 | $ (34) |

| | December 31, 2021 | | | | | |
|---|---|---|---|---|---|---|
| | Less Than 12 Months | | 12 Months or Longer | | Total | |
| | Fair Value | Unrealized Losses | Fair Value | Unrealized Losses | Fair Value | Unrealized Losses |
| Commercial paper | $ 47,425 | $ (34) | $ — | $ — | $ 47,425 | $ (34) |
| Corporate bonds | 12,573 | (7) | — | — | 12,573 | (7) |
| Total marketable securities | $ 59,998 | $ (41) | $ — | $ — | $ 59,998 | $ (41) |

The Company evaluated its securities for credit losses and considered the decline in market value to be primarily attributable to current economic and market conditions and not to a credit loss or other factors. Additionally, the Company does not intend to sell the securities in an unrealized loss position and does not expect they will be required to sell the securities before recovery of the unamortized cost basis. As of December 31, 2022 and 2021, an allowance for credit losses had not been recognized. Given the Company's intent and ability to hold such securities until recovery, and the lack of significant change in credit risk of these investments, the Company does not consider these marketable securities to be impaired as of December 31, 2022 and 2021.

There were no realized gains or losses on marketable securities for the years ended December 31, 2022 and 2021. Interest on marketable securities is included in interest income. Accrued interest receivable on available-for-sale debt securities totaled $0.1 million and $0.1 million as of December 31, 2022 and 2021, respectively, and is excluded from the estimate of credit losses.

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

| | December 31, | |
|---|---|---|
| | 2022 | 2021 |
| Due in one year or less | $ 20,848 | $ 77,986 |
| Due in 1 - 2 years | — | — |
| Total marketable securities | $ 20,848 | $ 77,986 |

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

## 5. Property and Equipment, Net

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

| | December 31, | |
|---|---|---|
| | 2022 | 2021 |
| Laboratory equipment | $ 2,257 | $ 2,245 |
| Furniture and office equipment | 520 | 520 |
| Computer equipment | 73 | 54 |
| Software | 121 | 139 |
| Leasehold improvements | 4,393 | 4,393 |
| Property and equipment, gross | 7,364 | 7,351 |
| Less: Accumulated depreciation and amortization | (4,144) | (2,802) |
| Property and equipment, net | $ 3,220 | $ 4,549 |

Depreciation and amortization expense for the years ended December 31, 2022, 2021, and 2020 was $1.4 million, $1.4 million, and $1.0 million, respectively. All of the Company's long-lived assets are located in the United States.

## 6. Accrued and Other Current Liabilities

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

| | December 31, | |
|---|---|---|
| | 2022 | 2021 |
| Accrued compensation | $ 4,589 | $ 4,988 |
| Accrued contracted research and development costs | 6,972 | 5,995 |
| Accrued professional and consulting fees | 946 | 2,264 |
| Other | 330 | 783 |
| Total accrued and other current liabilities | $ 12,837 | $ 14,030 |

## 7. Leases

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

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

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

| | Classification | December 31, 2022 | December 31, 2021 |
|---|---|---|---|
| **Assets** | | | |
| Operating | Operating lease right-of-use assets | $ 3,430 | $ 3,806 |
| Finance | Other non-current assets | 597 | 798 |
| Total leased assets | | 4,027 | 4,604 |
| | | | |
| **Leases** | | | |
| Current | | | |
| Operating | Operating lease liabilities | 625 | 436 |
| Finance | Accrued and other current liabilities | 16 | 418 |
| Non-current | | | |
| Operating | Non-current operating lease liabilities | 4,004 | 4,608 |
| Finance | Other non-current liabilities | — | 16 |
| Total lease liabilities | | $ 4,645 | $ 5,478 |

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

| | December 31, 2022 | December 31, 2021 |
|---|---|---|
| Lease term (years) | | |
| Operating leases | 5.3 | 6.3 |
| Finance leases | 0.6 | 0.5 |
| | | |
| Discount rate | | |
| Operating leases | 10.6% | 10.7% |
| Finance leases | 10.2% | 6.7% |

The following table summarizes the lease costs pertaining to the Company's operating leases (in thousands):

| | Year Ended December 31, 2022 | 2021 | 2020 |
|---|---|---|---|
| Operating lease cost | $ 910 | $ 991 | $ 1,258 |
| Variable lease cost | 472 | 519 | 665 |
| Total lease cost | $ 1,382 | $ 1,510 | $ 1,923 |

Cash paid for amounts included in the measurement of operating lease liabilities during the years ended December 31, 2022 and 2021 was $0.9 million and $1.1 million, respectively, and was included within net cash used in operating activities in the cash flows.

The maturities of the Company's operating and finance lease liabilities as of December 31, 2022 were as follows (in thousands):

| | Operating Leases | Finance Leases |
|---|---|---|
| 2023 | $ 1,078 | $ 16 |
| 2024 | 1,103 | — |
| 2025 | 1,129 | — |
| 2026 | 1,163 | — |
| 2027 | 1,198 | — |
| Thereafter | 403 | — |
| Total lease payments | 6,074 | 16 |
| Less: | | |
| Imputed interest | (1,445) | — |
| Total | $ 4,629 | $ 16 |

## 8. Stockholders' Equity

The Company is authorized to issue 510,000,000 shares of capital stock of which 500,000,000 shares are designated as common stock and 10,000,000 shares are designated as preferred stock, all with a par value of $0.0001 per share. Each holder of common stock is entitled to one vote for each share of common stock held. The Company's common stock is not entitled to preemptive rights, and is not subject to conversion, redemption or sinking fund provisions. Subject to preferences that may apply to any shares of preferred stock outstanding at the time, the holders of common stock are entitled to receive dividends out of funds legally available if the board of directors, in its discretion, determines to issue dividends and then only at the times and in the amounts that the board of directors may determine. As of December 31, 2022 and 2021, no common stock dividends had been declared by the board of directors and there were no shares of preferred stock outstanding.

### *Registered Direct Offering*

In May 2022, the Company issued and sold 10,752,688 shares of common stock at an offering price of $1.60 per share and pre-funded warrants to purchase up to 17,372,312 shares of common stock at an offering price of $1.5999 per warrant (representing the price per share of common stock sold in the offering minus the $0.0001 exercise price per warrant) in a registered direct offering pursuant to a shelf registration statement on Form S-3. The net proceeds to the Company from this offering were approximately $42.9 million, after deducting placement agent fees and offering costs of $2.1 million.

### *Follow-on Public Offerings*

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

In April 2020, the Company issued and sold 15,442,303 shares of common stock at a public offering price of $4.75 per share and pre-funded warrants to purchase up to 13,610,328 shares of common stock at a public offering price of $4.7499 per warrant in an underwritten public offering pursuant to a shelf registration statement on Form S-3. This includes the full exercise by the underwriters of their option to purchase up to 3,789,473 additional shares of common stock. The net proceeds to the Company from this public offering were $129.0 million, after deducting underwriting discounts and commissions of $8.2 million and offering costs of $0.8 million.

### *Pre-Funded Warrants*

In February 2019, April 2020 and May 2022, the Company issued pre-funded warrants to purchase the Company's common stock in underwritten public offerings at the offering price of the common stock, less the $0.0001 per share exercise price of each warrant. The warrants were recorded as a component of stockholders' equity within additional paid-in capital and have no expiration date. Per the terms of the warrant agreements, the outstanding warrants to purchase shares of common stock may not be exercised if the holder's ownership of the Company's common stock would exceed 4.99% ("Maximum Ownership Percentage") or 9.99% for certain holders. By written notice to the Company, each holder may increase or decrease the Maximum Ownership Percentage to any other percentage (not in excess of 19.99% for the majority of such warrants). The revised Maximum Ownership Percentage would be effective 61 days after the notice is received by the Company.

As of December 31, 2022, the following pre-funded warrants to purchase common stock were issued and outstanding:

| Issue Date | Expiration Date | Exercise Price | Number of Warrants Outstanding |
|---|---|---|---|
| February 2019 | None | $ 0.0001 | 3,750,000 |
| April 2020 | None | $ 0.0001 | 11,860,328 |
| May 2022 | None | $ 0.0001 | 13,281,250 |
| Total pre-funded warrants | | | 28,891,578 |

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

In April 2020, the Company entered into a new sales agreement with JonesTrading Institutional Services LLC, as sales agent, to issue and sell shares of its common stock for an aggregate offering price of $60.0 million under an at-the-market ("2020 ATM") offering program. In the fourth quarter of 2020, the Company issued and sold 3,245,077 shares of common stock under the 2020 ATM for gross proceeds of $25.3 million, resulting in net proceeds of $24.6 million, after deducting underwriting discounts, commissions, and offering costs.

**9. Strategic License Agreements**

***Immedica Pharma AB License and Development Agreement***

On March 21, 2021, the Company entered into an exclusive license and supply agreement with Immedica Pharma AB ("Immedica"). By entering into this agreement, the Company agreed to provide Immedica the following goods and services:

i. Deliver an exclusive, sublicensable, license and know-how (the "License") to develop and commercialize pegzilarginase (the "Product") in the territory comprising the members states of the European Economic Area, United Kingdom, Switzerland, Andorra, Monaco, San Marino, Vatican City, Turkey, Saudi Arabia, United Arab Emirates, Qatar, Kuwait, Bahrain, and Oman (the "Territory");

ii. Complete the global pivotal PEACE (Pegzilarginase Effect on Arginase 1 Deficiency Clinical Endpoints) Phase 3 trial ("PEACE Trial") and related Biologics License Application ("BLA") package to file with the United States Food and Drug Administration ("FDA"), which will be leveraged by Immedica in obtaining the necessary regulatory approvals in the Territory; and

iii. Perform a Pediatric Investigation Plan trial ("PIP Trial") in order for Immedica to be able to receive certain regulatory approvals within the Territory.

In addition, the Company and Immedica formed a Joint Steering Committee ("JSC") to provide oversight to the activities performed under the agreement; however, the substance of the Company's participation in the JSC does not represent an additional promised service, but rather, a right of the Company to protect its own interests in the arrangement.

Further, the Company agreed to supply to Immedica, and Immedica agreed to purchase from the Company, substantially all commercial requirements of the Product. The terms of the agreement do not provide for either (i) an option to Immedica to purchase the Product from the Company at a discount from the standalone selling price or (ii) minimum purchase quantities. Finally, Immedica will bear (i) all costs and expenses for any development or commercialization of the Product in the Territory subject to the License exclusive of the Company's promised goods and services summarized above and (ii) all costs and fees associated with applying for regulatory approval of the Product in the Territory. In July 2021, the Company modified the agreement with Immedica to provide certain additional services in relation to the PEACE Phase 3 Trial and BLA package performance obligation in exchange for the reimbursement of up to $3.0 million of the actual costs incurred in relation to such incremental services.

The Company received a non-refundable payment of $21.5 million and Immedica agreed to provide payment of 50% of the Company's costs incurred in performing the PIP Trial up to a maximum of $1.8 million. In addition, the Company has the ability to receive additional payments under the agreement of up to approximately $120.8 million in regulatory and commercial milestone payments, assuming an exchange rate of $1.07 to €1.00. The Company is also entitled to receive royalties in the mid-20 percent range on net sales of the Product in the Territory.

The Company concluded that Immedica meets the definition to be accounted for as a customer because the Company is delivering intellectual property and other services within the Company's normal course of business, in which the parties are not jointly sharing the risks and rewards. Therefore, the Company concluded that the promises summarized above represent transactions with a customer within the scope of ASC 606. The Company determined that the following promises represent distinct promised services, and therefore, performance obligations: (i) the License, (ii) the PEACE Trial and BLA package, and (iii) the PIP Trial.

Specifically, in making these determinations, the Company considered the following factors:

- As of inception of the agreement, the Company had completed the Phase 1/2 clinical trial related to the Product and were conducting the ongoing PEACE Trial. Accordingly, the Company is not promising, nor expecting, to perform additional research and development activities pursuant to the agreement that would either significantly modify, customize or be considered highly interdependent or interrelated with pegzilarginase.

- The License represents functional intellectual property given the functionality of the License is not expected to change substantially as a result of the company's ongoing activities.
- The services necessary to complete the PEACE Trial, BLA package and PIP Trial could be performed by other parties.

Given that Immedica is not obligated to purchase any minimum amount or quantities of the Product, the supply of the Product for commercial use to Immedica was determined to be an option for Immedica, rather than a performance obligation of the Company at contract inception and will be accounted for if and when exercised. The Company also determined that Immedica's option to purchase the Product does not create a material right as the expected pricing is not at a discount.

The Company determined that the upfront fixed payment amount of $21.5 million must be included in the transaction price. Additionally, the Company determined at inception of the arrangement that 50% of the estimated costs to be incurred in relation to the PIP Trial exceeded $1.8 million and included the full reimbursement amount of $1.8 million in the transaction price. Upon subsequent re-evaluation due to changing facts and circumstances, the Company determined the estimated costs are now less than the maximum allowable reimbursement and a portion of the variable consideration was constrained, which did not materially impact the revenue recognized to date. Additionally, upon the modification of the agreement in July 2021, the Company determined that the estimated costs to perform the additional services related to the PEACE Trial and BLA package exceeds the maximum allowable reimbursement of $3.0 million. Therefore, the Company included an estimated total of $3.6 million that will be due in relation to the PIP Trial, PEACE Trial, and BLA package in the transaction price and it is probable that a significant reversal will not occur in the future. In total, the modified transaction price was determined to be $25.1 million.

The Company has allocated $9.6 million and $3.5 million of the modified transaction price to the PEACE Trial and BLA package and PIP Trial performance obligations, respectively, based on the stand-alone selling prices ("SSP"), which was based on the estimated costs that a third-party would charge in performing such services on a stand-alone basis. The SSP for the License was established at inception of the arrangement using a residual value approach due to the uniqueness of and lack of observable data related to the License, and without a specific analog from which to make reliable estimates, resulting in an allocation of $12.0 million.

The potential regulatory milestone payments that the Company is eligible to receive were excluded from the transaction price, as the milestone amounts were fully constrained based on the probability of achievement, since the milestones relate to successful achievement of certain regulatory approvals, which might not be achieved. The Company determined that the royalties and commercial milestone payments relate predominantly to the license of intellectual property and are therefore excluded from the transaction price under the sales- or usage-based royalty exception of ASC 606. The Company will reevaluate the transaction price, including all constrained amounts, at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, the Company will adjust its estimate of the transaction price as necessary. The Company will recognize the royalties and commercial milestone payments as revenue when the associated sales occur, and relevant sales-based thresholds are met. The Company assessed the arrangement with Immedica and concluded that a significant financing component does not exist.

The Company recognized revenue allocated to the License performance obligation at a point in time and upon transfer of the License. The Company completed the transfer of the know-how necessary for Immedica to benefit from the License in June 2021 and recognized $12.0 million of revenue at that time. The development fee allocated to the PEACE Trial, BLA package and PIP Trial performance obligations will be recognized over time using an input method of costs incurred related to the performance obligations.

For the year ended December 31, 2022, the Company recognized revenue of $2.3 million related to the PEACE Trial and BLA package performance obligation using a cost to cost model. The Company recognized revenue of $6.7 million related to the PEACE Trial and BLA package performance obligation using a cost to cost model and $12.0 million related to the transfer of the License for the year ended December 31, 2021 and no revenue for the year ended December 31, 2020. As of December 31, 2022, the Company has recorded deferred revenue of $2.7 million associated with the license and supply agreement with Immedica, of which $0.5 million is classified as current. As of December 31, 2021, the Company had recorded deferred revenue of $3.6 million associated with the license and supply agreement with Immedica, of which $2.4 million was classified as current.

**Contract Balances from Customer Contract**

The timing of revenue recognition, billings and cash collections results in contract assets and contract liabilities on the balance sheets. The Company recognizes license and development receivables based on billed services, which are derecognized upon reimbursement. When consideration is received, or such consideration is unconditionally due, from a customer prior to transferring goods or services to the customer under the terms of a contract, a contract liability is recorded. Contract liabilities are recognized as revenue after control of the goods or services is transferred to the customer and all revenue recognition criteria have been met.

The following table presents changes in the Company's contract liabilities for the periods presented (in thousands):

| Year Ended December 31, 2021 | December 31, 2021 | Additions | Deductions | December 31, 2022 |
|---|---|---|---|---|
| Contract liabilities: | | | | |
| Deferred revenue | $ 3,576 | $ 1,449 | $ (2,329) | $ 2,696 |

The Company had no contract assets during the years ended December 31, 2022, 2021 and 2020 and no contract liabilities during the year ended December 31, 2020.

***University of Texas at Austin License Agreement***

In December 2013, two of the Company's 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 (the "University") for certain intellectual property owned by the University related to cystinase and methioninase. In January 2017, the Company and the University entered into an Amended and Restated Patent License Agreement (the "Restated License"), which consolidated the two license agreements, revised certain obligations, and licensed additional patent applications and invention disclosures to us. The Restated License was amended in August 2017, December 2017, and December 2018 to revise diligence milestones and license additional patent applications, including our program candidates under the pegtarviliase and Cystinuria Programs.

Pursuant to the terms of the Restated License, the Company may be required to pay the University up to $6.4 million in milestone payments based on the achievement of certain development milestones, including clinical trials and regulatory approvals, the majority of which are due upon the achievement of later development milestones, including a $5.0 million payment due on regulatory approval of a product and a $0.5 million payment payable on final regulatory approval of a product for a second indication. In addition, the Company is required to pay the University a low single-digit royalty on worldwide-net sales of products covered under 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.

In the year ended December 31, 2022, the Company paid $0.1 million in milestone payments pursuant to the Restated License. For the years ended December 31, 2021 and 2020, the Company paid $0.1 million in license fees annually.

**10. Stock-Based Compensation**

***2015 Equity Incentive Plan***

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

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

As of December 31, 2022, a total of 94,639 shares of common stock are subject to options outstanding under the 2015 Plan and will become available under the 2016 Equity Incentive Plan ("2016 Plan") to the extent the options are forfeited or lapse unexercised.

***2016 Equity Incentive Plan***

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

In October 2018, the 2016 plan was amended to increase the number of shares of common stock reserved for issuance thereunder by 1,759,602 shares, extend the term of the 2016 Plan through August 7, 2028, and provide for an automatic increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the plan equal to (a) 4.0% of the number of issued and outstanding shares of common stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the board each year. As a result of the operation of each of these provisions, on January 1, 2022, 2021, and 2020, an additional 1,974,205, 1,918,363, and 1,163,377 shares, respectively, became available for issuance under the 2016 Plan.

As of December 31, 2022, the total number of shares reserved for issuance under the 2016 Plan was 10,818,148, of which 7,978,070 shares were subject to outstanding option awards and restricted unit awards.

***2018 Equity Inducement Plan***

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

As of December 31, 2022, the total number of shares reserved for issuance under the 2018 Plan was 1,100,000, of which 311,000 shares were subject to outstanding option awards.

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

***CEO Inducement Grant***

In November 2022, the Company granted 1.9 million non-qualified stock options to the new Chief Executive Officer in a stand alone inducement grant. The first 25% of these options vest on the one year anniversary of the grant, and the remaining 75% vest in equal amounts over 48 months following the one year anniversary date and are exercisable for a term of ten years.

The following table summarizes employee and non-employee stock option activity for the year ended December 31, 2022:

| | Shares Issuable Under Options | Weighted Average Exercise Price | Weighted Average Remaining Contractual Term (in years) | Aggregate Intrinsic Value (in thousands) |
|---|---|---|---|---|
| **Outstanding as of December 31, 2021** | 6,607,587 | $ 7.56 | 7.90 | $ 328 |
| Granted | 5,879,991 | 1.80 | | |
| Exercised | — | — | | |
| Forfeited | (2,360,531) | 6.14 | | |
| **Outstanding as of December 31, 2022** | 10,127,047 | $ 4.55 | 6.72 | $ 2 |
| **Options vested and expected to vest as of December 31, 2022** | 9,944,309 | $ 4.50 | 6.78 | $ 2 |
| **Options exercisable as of December 31, 2022** | 4,086,256 | $ 6.84 | 4.93 | $ — |

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

For the years ended December 31, 2022, 2021, and 2020, the weighted-average grant date fair value of options granted was $1.80, $4.96, and $4.68, respectively. No options were exercised in the year ended December 31, 2022. The total intrinsic value of options exercised during the years ended December 31, 2021, and 2020 was $0.7 million and $0.4 million, respectively.

There were no stock options issued to non-employees during the years ended December 31, 2022, 2021, and 2020. For the year ended December 31, 2020, 1,663 non-employee stock options vested in the period. For the years ended December 31, 2022 and 2021, no non-employee stock options vested in the period.

***2016 Employee Stock Purchase Plan***

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

In June 2018, the 2016 ESPP was amended to provide for an automatic annual increase in the number of shares reserved for issuance thereunder on January 1 of each year for the remaining term of the year equal to (a) 1.0% of the number of issued and outstanding shares of common stock on December 31 of the immediately preceding year, or (b) a lesser amount as approved by the board of directors each year. As a result of the operation of this provision, on January 1, 2022, 2021 and 2020, an additional 493,551, 479,590, and 290,844 shares, respectively, became available for issuance under the 2016 ESPP. As of December 31, 2022, the reserve remaining and available for future issuance under the 2016 ESPP was 1,216,647 shares.

In February 2023, the 2016 ESPP was amended to increase the maximum shares purchased during any one period from 2,000 shares to 10,000 shares or a lesser amount determined by the board of directors.

***Restricted Common Stock Units***

The Company granted 228,200 restricted stock units ("RSUs") during the year ended December 31, 2020 to certain employees with regulatory, commercial, and clinical milestones in addition to a service condition. There were no RSUs granted for the years ended December 31, 2022 and 2021.

As of December 31, 2022, the performance conditions of the granted RSUs were not probable of being achieved. If and when the performance milestones are deemed probable of being achieved within the required time frame, the Company may recognize up to $1.2 million of stock-based compensation for the remaining unvested RSUs as of December 31, 2022.

The following table summarizes employee restricted stock activity for the year ended December 31, 2022:

| | Shares | Weighted Average Grant Date Fair Value |
|---|---|---|
| **Unvested restricted stock units as of December 31, 2021** | 190,000 | $ 8.13 |
| Granted | — | — |
| Vested | — | — |
| Forfeited | (48,500) | 8.13 |
| **Unvested restricted stock units as of December 31, 2022** | 141,500 | $ 8.13 |

There were no RSUs granted to non-employees during the years ended December 31, 2022, 2021, and 2020.

***Stock-Based Compensation Expense***

Total stock-based compensation expense recognized from the Company's equity incentive plans, 2018 Plan, and the 2016 ESPP for the years ended December 31, 2022, 2021, and 2020 was as follows (in thousands):

| | Year Ended December 31, | | | | | |
|---|---|---|---|---|---|---|
| | 2022 | | 2021 | | 2020 | |
| | Employees | Non-Employees | Employees | Non-Employees | Employees | Non-Employees |
| Research and development | $ 2,591 | $ — | $ 2,723 | $ — | $ 2,168 | $ 36 |
| General and administrative | 4,520 | — | 5,315 | — | 4,052 | — |
| Total stock-based compensation expense | $ 7,111 | $ — | $ 8,038 | $ — | $ 6,220 | $ 36 |

No related tax benefits were recognized for the years ended December 31, 2022, 2021, and 2020 (see Note 11).

The employee and non-employee awards contain both performance and service-based vesting conditions. No expense was recognized for the unvested employee and non-employee awards with only a performance condition for the years ended December 31, 2022, 2021, and 2020. The performance-based vesting conditions represent specific performance targets. Compensation expense for employee and non-employee share-based payment awards with performance conditions is recognized when the performance condition is deemed probable of achievement.

As of December 31, 2022, the Company had an aggregate of $11.6 million of unrecognized stock-based compensation expense for options outstanding, which is expected to be recognized over a weighted average period of 1.6 years.

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

***Expected Term***

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

***Expected Volatility***

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

calculated expected term of the stock-based awards. The Company intends to consistently apply this process using the same or similar comparable entities until a sufficient amount of historical information regarding the volatility of the Company's own share price becomes available.

***Risk-Free Interest Rate***

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

***Expected Dividend***

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

***Valuation of Stock Options and 2016 ESPP***

The fair value of the stock options granted under the 2018 Plan, 2016 Plan, 2015 Plan and the CEO inducement grant, as well as 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, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| **Stock Options Granted** | | | |
| Expected term (in years) | 6.00 | 5.99 | 6.10 |
| Expected volatility | 84% | 83% | 76% |
| Risk-free interest | 2.93% | 0.88% | 1.06% |
| Dividend yield | 0% | 0% | 0% |
| **2016 ESPP** | | | |
| Expected term (in years) | 0.49 | 0.50 | 0.50 |
| Expected volatility | 84% | 86% | 76% |
| Risk-free interest | 1.95% | 0.08% | 0.75% |
| Dividend yield | 0% | 0% | 0% |

## 11. Defined Contribution Plan

The Company sponsors a 401(k) retirement plan in which substantially all of its full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. During the years ended December 31, 2022, 2021, 2020, the Company provided $0.6 million, $0.6 million, and $0.5 million, respectively, in contributions to the plan.

## 12. Income Taxes

The following table summarizes the (loss) income before income tax expense by jurisdiction for the periods indicated:

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| Domestic | $ (84,113) | $ (65,940) | $ (80,893) |
| Foreign | 162 | 280 | — |
| Loss before income tax expense | $ (83,951) | $ (65,660) | $ (80,893) |

For the year ended December 31, 2022, the Company recognized an income tax expense of $0.1 million, related to foreign subsidiaries refund from research client and foreign subsidiaries income tax expense. For the year ended December 31, 2021, the Company recognized an income tax expense of $0.1 million, related to foreign subsidiaries income tax expense and the Texas margins tax. For the year ended December 31, 2020, 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, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| Tax provision derived by applying the federal statutory rate to income before income taxes | $ (17,630) | $ (13,789) | $ (16,988) |
| Permanent differences and other | 1,042 | 1,002 | 482 |
| Federal tax credits | (3,559) | (3,815) | (3,905) |
| State tax credits | (640) | (152) | (251) |
| Effect of tax rate on foreign jurisdiction | 42 | (5) | — |
| Change in the valuation allowance | 20,609 | 16,900 | 20,662 |
| Income tax (benefit) expense | $ (136) | $ 141 | $ — |

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

| | December 31, | |
|---|---|---|
| | 2022 | 2021 |
| Deferred tax assets | | |
| Net operating loss carryforward | $ 68,917 | $ 64,531 |
| Intangible assets | 11,149 | 57 |
| Deferred revenue | 566 | — |
| Accrued expense | 668 | 846 |
| Stock-based compensation | 3,293 | 2,767 |
| Federal tax credits | 21,914 | 18,579 |
| State tax credits | 1,631 | 991 |
| Other | 190 | 220 |
| Total deferred tax assets | 108,328 | 87,991 |
| Deferred tax liabilities | | |
| Depreciable assets | (676) | (948) |
| Total deferred tax liabilities | (676) | (948) |
| Less: Valuation allowance | (107,652) | (87,043) |
| Deferred tax assets, net | $ — | $ — |

The Company has established a full federal and state valuation allowance equal to the net deferred tax assets due to uncertainties regarding the realization of the deferred tax asset based on the Company's lack of earnings history. The valuation allowance increased by $20.6 million, $16.9 million, and $20.7 million during the years ended December 31, 2022, 2021, and 2020, respectively, primarily due to continuing loss from operations.

As of December 31, 2022 and 2021, the Company had U.S. net operating loss carryforwards ("NOL") of $328.2 million and $307.3 million, respectively. As of December 31, 2022 and 2021, the Company had U.S. tax credit carryforwards of $21.9 million and $18.6 million, respectively, and state tax credit carryforwards of $1.6 million and $1.0 million, respectively. Of the net operating loss and tax credit carryforwards, $58.4 million and $21.9 million, respectively, will expire in 2033, if not utilized. Any remaining net operating loss will carry forward indefinitely and can be utilized to offset up to 80% of the taxable income in any tax year. The net operating loss and credit carryforwards are subject to Internal Revenue Service adjustments until the statute closes on the year the net operating loss or tax credits are utilized.

The Company has not completed a study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since the Company's formation due to the complexity and cost associated with such a study, and the fact that there may be additional such ownership changes in the future. If the Company has experienced an ownership change at any time since its formation, utilization of the NOL or research and development 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 eight wholly owned U.S. subsidiary corporations. The SRLY rules limit the consolidated group's use of a subsidiary corporation's net operating losses to the amount of income generated by the subsidiary corporation after it becomes a member of the group. Any limitation may result in expiration of a portion of the NOL or research and development 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 is subject to examination by taxing authorities in its significant jurisdictions for the 2018 and subsequent years. However, due to NOL and tax attribute carryovers, the taxing authorities have the ability to adjust the NOLs and other tax attributes related to closed years. As of December 31, 2022 and 2021, there were no amounts recorded for uncertain tax positions. As of December 31, 2022, undistributed earnings of the Company's newly incorporated foreign subsidiaries are immaterial. Under the Global Intangible Low-Taxed Income ("GILTI") provisions of the 2017 Tax Cuts and Jobs Act, U.S. income taxes have been incurred on the undistributed earnings of the foreign subsidiaries and therefore, the tax impact upon distribution is limited to state income and withholding taxes and is not material.

## 13. Net Loss Per Share

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

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

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| Options to purchase common stock | 8,658,285 | 6,621,457 | 5,049,435 |
| Unvested restricted stock units | 174,568 | 199,379 | 105,995 |

The following is a reconciliation of the shares used as the denominator for the calculation of basic and diluted net loss per share:

| | Year Ended December 31, | | |
|---|---|---|---|
| | 2022 | 2021 | 2020 |
| Weighted average common shares | 57,691,709 | 48,923,324 | 40,223,804 |
| Weighted average pre-funded warrants | 26,589,076 | 16,821,287 | 13,147,925 |
| Total basic and diluted weighted average shares | 84,280,785 | 65,744,611 | 53,371,730 |

## 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, 2022, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act are recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

### Management's Annual Report on Internal Control Over Financial Reporting

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

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

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management, with the participation of our principal executive officer and principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its 2013 Internal Control – Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2022, our internal control over financial reporting is effective based on those criteria.

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting. For as long as we remain a "smaller reporting company" as defined by Rule 12b-2 of the Exchange Act and report less than $100 million of annual revenues in our most recent fiscal year, 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, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

## ITEM 9B. OTHER INFORMATION

None.

## ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

None.

## PART III

### ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated herein by reference from the applicable information set forth in "Board of Directors and Committees of The Board; Corporate Governance Standards and Director Independence," "Election of Directors" and "Executive Officers" of our Proxy Statement with respect to our 2023 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 from the applicable information set forth in "Executive Compensation" of our Proxy Statement with respect to our 2023 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 from the applicable information set forth in "Security Ownership of Certain Beneficial Owners and Management" of our Proxy Statement with respect to our 2023 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 from the applicable information set forth in "Related Party Transactions" of our Proxy Statement with respect to our 2023 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 from the applicable information set forth in "Ratification of Appointment of Independent Registered Public Accounting Firm" of our Proxy Statement with respect to our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

## PART IV

## ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

The following documents are filed as part of this report:

### 1. Financial Statements

See Index to Financial Statements at Item 8 herein.

### 2. Financial Statement Schedules

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

### 3. Exhibits

| Exhibit Number | Description of Document | Incorporate by Reference | | | | Filed Herewith |
|---|---|---|---|---|---|---|
| | | Form | File No. | Date of Filing | Exhibit No. | |
| 3.1 | Restated Certificate of Incorporation | S-1/A | 333-205001 | 9/14/2015 | 3.2 | |
| 3.2 | Amended and Restated Bylaws | 8-K | 001-37722 | 12/19/2022 | 3.1 | |
| 4.1 | Form of Common Stock Certificate | S-1/A | 333-205001 | 9/14/2015 | 4.1 | |
| 4.2 | Form of Pre-Funded Warrants 2019 | 8-K | 001-37722 | 2/7/2019 | 4.1 | |
| 4.3 | Description of the Registrant's securities | 10-K | 001-37722 | 3/18/2021 | 4.3 | |
| 4.4 | Form of Pre-Funded Warrants 2020 | 8-K | 001-37722 | 4/28/2020 | 4.1 | |
| 4.5 | Registration Rights Agreement, dated March 16, 2021, by and among the Registrant and Baker Brothers Life Sciences, L.P. and 667, L.P. | 10-K | 001-37722 | 3/18/2021 | 4.5 | |
| 4.6 | Form of Pre-Funded Warrants 2022 | 8-K | 001-37722 | 5/6/2022 | 4.1 | |
| 10.1 | Form of Amended and Restated Indemnification Agreement | 10Q | 001-37722 | 8/9/2018 | 10.1 | |
| 10.2‡ | 2015 Equity Incentive Plan and forms of award agreements | S-1 | 333-205001 | 6/16/2015 | 10.2 | |
| 10.3‡ | 2016 Equity Incentive Plan and forms of award agreements, as amended | 10Q | 001-37722 | 11/8/2018 | 10.2 | |
| 10.4‡ | 2016 Employee Stock Purchase Plan and forms of award agreements, as amended | 10-K | 001-37722 | 3/7/2019 | 10.4 | |
| 10.5‡ | 2018 Equity Inducement Plan | S-8 | 333-223614 | 3/13/2018 | 99.2 | |
| 10.6‡ | Form of Stock Restriction Agreement | S-1 | 333-205001 | 6/16/2015 | 10.5 | |
| 10.7‡ | Form of Severance Agreement | 8-K | 001-37722 | 4/16/2018 | 10.1 | |
| 10.8† | Sponsored Research Agreement No. UTA13-001113, dated December 24, 2013, between The University of Texas at Austin and Aeglea BioTherapeutics, Inc., Aeglea Development Company, Inc., AERase, Inc., AEMase, Inc., AECase, Inc., AE4ase, Inc., AE5ase, Inc. and AE6ase., Inc., as amended | 10-Q | 001-37722 | 11/7/2017 | 10.3 | |

| Exhibit Number | Description of Document | Incorporate by Reference | | | | Filed Herewith |
|---|---|---|---|---|---|---|
| | | Form | File No. | Date of Filing | Exhibit No. | |
| 10.9 | Office Lease, dated November 24, 2014, between Barton Oaks Office Center, LLC and the Registrant | S-1 | 333-205001 | 6/16/2015 | 10.11 | |
| 10.10 | First Amendment to Office Lease and Assignment and Assumption of Lease dated September 20, 2016 to Office Lease dated November 24, 2014, between Barton Oaks Office Center, LLC, Aeglea Development Company, Inc., and Aeglea BioTherapeutics, Inc. | 10-Q | 001-37722 | 11/9/2016 | 10.1 | |
| 10.11† | Amended and Restated Patent License Agreement No. PM1401501, dated January 31, 2017, between the Registrant and The University of Texas at Austin on behalf of the Board of Regents of the University of Texas system | 10-K | 001-37722 | 3/7/2019 | 10.12 | |
| 10.12† | Cancer Research Grant Contract, dated June 15, 2015, between AERase, Inc. and the Cancer Prevention Research Institute of Texas | S-1 | 333-205001 | 6/16/2015 | 10.15 | |
| 10.13‡ | Offer Letter, dated July 18, 2018, by and between the Registrant and Anthony G. Quinn | 8-K | 001-37722 | 7/23/2018 | 10.1 | |
| 10.14‡ | Severance Agreement, dated July 18, 2018, by and between the Registrant and Anthony G. Quinn | 8-K | 001-37722 | 7/23/2018 | 10.2 | |
| 10.15† | Master Services Agreement, dated November 26, 2018, between the Registrant, Fujifilm Diosynth Biotechnologies UK Limited, Fujifilm Diosynth Biotechnologies Texas, LLC, and Fujifilm Diosynth Biotechnologies U.S.A, Inc. | 10-K | 001-37722 | 3/7/2019 | 10.18 | |
| 10.16 | Lease Agreement dated April 30, 2019, between Las Cimas Owner LP and the Registrant | 10-Q | 001-37722 | 5/7/2019 | 10.1 | |
| 10.17‡ | Transition Agreement, dated August 24, 2022, by and between the Registrant and Anthony Quinn | | | | | X |
| 10.18‡ | License and Supply Agreement, dated March 21, 2021, by and between the Registrant and Immedica Pharma AB | 10-Q | 001-37722 | 5/10/2021 | 10.1 | |
| 10.19‡ | Offer Letter, dated June 14, 2021 issued by the Registrant to Mr. Jonathan Alspaugh | 10-K | 001-37722 | 03/08/2022 | 10.20 | |
| 10.20‡ | Severance Agreement dated July 6, 2021 by and between the Registrant and Mr. Jonathan Alspaugh | 10-K | 001-37722 | 03/08/2022 | 10.21 | |
| 10.21‡ | Offer Letter, dated November 8, 2022, by and between the Registrant and Jeffrey M. Goldberg | | | | | X |
| 10.22‡ | Severance Agreement, dated November 8, 2022, by and between the Registrant and Jeffrey M. Goldberg | | | | | X |
| 10.23‡ | Offer Letter, dated October 11, 2019, by and between the Registrant and Michael Hanley | | | | | X |
| 10.24‡ | Severance Agreement, dated October 21, 2019, by and between the Registrant and Michael Hanley | | | | | X |
| 21.1 | Subsidiaries of the Registrant | | | | | X |

| Exhibit Number | Description of Document | Incorporate by Reference | | | | Filed Herewith |
|---|---|---|---|---|---|---|
| | | Form | File No. | Date of Filing | Exhibit No. | |
| 23.1 | Consent of independent registered public accounting firm | | | | | X |
| 24.1 | Power of Attorney. Reference is made to the signature page hereto | | | | | X |
| 31.1 | Certification of the Principal Executive Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934 | | | | | X |
| 31.2 | Certification of the Principal Financial Officer pursuant to Rule 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934 | | | | | X |
| 32.1(1) | Certification of the Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 | | | | | X |
| 32.2(1) | Certification of the Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 | | | | | X |
| 101.INS | Inline XBRL Instance Document - the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document | | | | | X |
| 101.SCH | Inline XBRL Taxonomy Extension Schema Document | | | | | X |
| 101.CAL | Inline XBRL Taxonomy Extension Calculation Linkbase Document | | | | | X |
| 101.DEF | Inline XBRL Taxonomy Extension Definition Linkbase Document | | | | | X |
| 101.LAB | Inline XBRL Taxonomy Extension Labels Linkbase Document | | | | | X |
| 101.PRE | Inline XBRL Taxonomy Extension Presentation Linkbase Document | | | | | X |
| 104 | The cover page of this Annual Report on Form 10-K for the year ended December 31, 2022, formatted in Inline XBRL and contained in Exhibit 1010 | | | | | |

† 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.

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

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

None.

## SIGNATURES

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

Date: March 2, 2023

AEGLEA BIOTHERAPEUTICS, INC.

By: /s/ Jeffrey Goldberg
Jeffrey Goldberg
*President and Chief Executive Officer*
*(Principal Executive Officer)*

## POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Jeffrey Goldberg and Jonathan Alspaugh, jointly and severally, his attorneys-in-fact, each with the power of substitution, for him 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/Jeffrey Goldberg<br>Jeffrey Goldberg | President and Chief Executive Officer<br>(Principal Executive Officer) | March 2, 2023 |
| /s/ Jonathan Alspaugh<br>Jonathan Alspaugh | Chief Financial Officer<br>(Principal Financial Officer and Principal Accounting Officer) | March 2, 2023 |
| /s/ Russell J. Cox<br>Russell J. Cox | Director | March 2, 2023 |
| /s/ Armen Shanafelt, Ph.D.<br>Armen Shanafelt, Ph.D. | Director | March 2, 2023 |
| /s/ Ivana Magovcevic-Liebisch, Ph.D.<br>Ivana Magovcevic-Liebisch, Ph.D. | Director | March 2, 2023 |
| /s/ V. Bryan Lawlis, Ph.D.<br>V. Bryan Lawlis, Ph.D. | Director | March 2, 2023 |
| /s/ Alison Lawton<br>Alison Lawton | Director | March 2, 2023 |
| /s/ Marcio Souza, M.B.A.<br>Marcio Souza, M.B.A. | Director | March 2, 2023 |
| /s/ Hunter C. Smith, M.B.A.<br>Hunter C. Smith, M.B.A. | Director | March 2, 2023 |