2022 ANNUAL REPORT

PassageBio

Life-transforming therapies

OUR VISION

To fulfill the promise of genetic medicine by developing transformative therapies for people with devastating CNS diseases

To Our Shareholders,

Reflecting on my first months since joining Passage Bio, 2022 was a year of change for the company. While change can be daunting, it is often necessary to clear a path toward progress. That progress is what Passage Bio is focused on achieving in 2023 as we advance our ambitious mission of delivering life-transforming gene therapies for people with devastating central nervous system (CNS) disorders.

The pursuit of medical innovation is rarely a straight path. Over the last year, our team was faced with making challenging decisions to streamline our organization and focus our preclinical and clinical programs. While difficult, these decisions have allowed us to weather a volatile financial market and focus on executing against our promising clinical programs for GM1 and FTD. With cash runway into 2025, we are in a stronger position to make thoughtful decisions in the best interest of our clinical programs and the patients we serve.

Fulfilling the bold promise of genetic medicine

Today, we are committed to advancing two ongoing clinical programs: PBGM01 for the treatment of GM1 gangliosidosis (GM1) and PBFT02 for the treatment of frontotemporal dementia caused by granulin mutations (FTD-GRN).

The potential for these two programs to significantly impact those living with CNS disorders was a key factor in my decision to join the company. We are thrilled to share that momentum in both programs is strong, and we anticipate delivering meaningful clinical data throughout this year.

Meeting the urgent patient need in GM1

We have made considerable progress in the development of PBGM01, our investigational gene therapy for the treatment of GM1 gangliosidosis, a rare and fatal pediatric CNS disorder with no approved disease-modifying therapies. PBGM01 could make a profound difference in the lives of infants with GM1, which sadly carries a life expectancy of only two to ten years. Over the last few months, we have been encouraged by interim data showing that PBGM01 was well-tolerated, had a positive safety profile and exerted a biological effect in all treated infantile GM1 patients. We also observed a strong dose-response effect in key biomarkers and are learning that earlier treatment may offer patients the greatest benefit.

Today, PBGM01 is the leading treatment under development for children suffering from GM1 and a critical source of hope for families affected by this disease. We look forward to executing against several important milestones in 2023, including reporting data from early infantile patients treated with a high dose and advancing the study to treat patients at a third, higher dose.

Advancing a differentiated gene therapy approach in FTD-GRN

In 2022, we initiated our second lead program evaluating PBFT02, an adeno-associated virus (AAV)-delivery gene therapy for adults with FTD-GRN, a form of early-onset dementia with no approved disease-modifying therapies. PBFT02 utilizes a proprietary construct to deliver a functional GRN gene encoding progranulin to the CNS of patients via intra-cisterna (ICM) injection. In preclinical studies, we observed that PBFT02 was able to increase levels of progranulin, the protein of interest, to higher-than-normal physiologic levels. We are excited by the potential therapeutic benefit of this one-time gene therapy approach. In August 2022, we dosed the first patient in our global Phase 1/2 upliFT-D clinical trial of PBFT02. Patient enrollment activities are progressing well, and we expect to share initial safety and biomarker data from Cohort 1 patients in the second half of this year.

Promising preclinical pipeline in adult CNS disorders

To further solidify our strategy for long-term growth, we have built a promising preclinical pipeline of candidates focused on addressing adult CNS disorders, including Amyotrophic Lateral Sclerosis (ALS) and Huntington's disease. These preclinical programs are supported by our strategic collaboration with the world-renowned University of Pennsylvania's Gene Therapy Program (GTP).

Delivering value for patients and shareholders

2022 was a consequential year for Passage Bio and the steps we have taken have set us up to meet key milestones. With a strong balance sheet to support our operations into 2025 and an exceptional team highly focused on execution, we are well positioned to deliver on our compelling value proposition to develop medicines that will transform the lives of patients and their families.

I want to express my gratitude to our dedicated team of employees, whose commitment and tenacity have been instrumental in the strong progress we have made, and our invaluable partnerships with scientists, healthcare providers and most of all, people living with CNS diseases and their families. The work we are doing together is more important than ever.

On behalf of all of us at Passage Bio, thank you for your continued support. It's an honor to lead this organization — I'm confident the best is yet to come.

Sincerely,

William Chou, M.D.
Chief Executive Officer

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022

OR

☐ **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 001-39231

PASSAGE BIO, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware **(State or other jurisdiction of incorporation or organization)**	**82-2729751** **(I.R.S. Employer Identification No.)**
One Commerce Square **2005 Market Street, 39th Floor** **Philadelphia, PA** **(Address of principal executive offices)**	**19103** **(Zip Code)**

(267) 866-0311
(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common stock	PASG	The Nasdaq Stock Market LLC (Nasdaq Global Select Market)

Securities registered pursuant to Section 12(g) of the 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 Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the issuer (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 common equity 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 $2.36 of the Registrant's common stock as reported on The Nasdaq Global Market, was approximately $100.6 million.

The number of shares of the registrant's common stock outstanding as of March 2, 2023, was 54,617,523.

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.

Passage Bio, Inc.

ANNUAL REPORT ON FORM 10-K

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements. All statements other than statements of historical facts contained in this Annual Report are forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "aim," "may," "will," "should," "expect," "forecast," "plan," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions, although not all forward-looking statements contain these words. All statements other than statements of historical fact contained in this Annual Report, including without limitation statements regarding our plans to develop and commercialize our product candidates, the timing and results of our ongoing or planned preclinical studies and clinical trials, risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, the timing of and our ability to obtain and maintain regulatory approvals, the clinical utility of our product candidates, our commercialization, marketing and manufacturing capabilities and strategy, our expectations about the willingness of healthcare professionals to use our product candidates, the sufficiency of our cash and cash equivalents, general economic, industry and market conditions, including rising interest rates and inflation, our activities to evaluate and pursue strategic alternatives following our determination to discontinue the advancement of certain product candidates, and the plans and objectives of management for future operations and capital expenditures are forward-looking statements.

The forward-looking statements in this Annual Report are only predictions and are based largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Annual Report and are subject to a number of known and unknown risks, uncertainties and assumptions, including those described under the sections in this Annual Report entitled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this Annual Report.

Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. We intend the forward-looking statements contained in this Annual Report to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act.

TRADEMARKS AND TRADENAMES

"PASSAGE BIO" is a registered trademark, and the PASSAGE BIO mark, the Passage Bio logo and all product names are our common law trademarks. All other service marks, trademarks and tradenames appearing in this prospectus are the property of their respective owners. Solely for convenience, the trademarks and tradenames referred to in this prospectus appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or the right of the applicable licensor to these trademarks and tradenames.

Summary of Risk Factors

Our business is subject to a number of risks and uncertainties, including those immediately following this summary. Some of these risks are:

- We are a clinical stage genetic medicines company with a history of operating losses, and we may not achieve or sustain profitability. We anticipate that we will continue to incur losses for the foreseeable future. Our limited operating history may make it difficult for you to evaluate our success to date and to assess our future viability;

- We will need to raise additional funding before we can expect to become profitable from any potential future sales of our products;

- We are early in our development efforts. Our business is dependent on our ability to advance our current and future product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them;

- The disorders we seek to treat have low incidence and prevalence and it may be difficult to identify patients with these diseases, which may lead to delays in enrollment for our trials or slower commercial revenue if approved;

- Preclinical and clinical development involve a lengthy and expensive process with an uncertain outcome. We may incur additional expenses or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our current product candidates or any future product candidates;

- Gene therapy is a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval;

- Our product candidates may cause undesirable and unforeseen side effects, which could delay or prevent their advancement into clinical trials or regulatory approval, limit the commercial potential or result in significant negative consequences;

- We currently rely exclusively on our collaboration with Penn for our preclinical research and development, including for discovering, preclinically developing and conducting all IND-enabling studies for our clinical product candidates and our near-term future pipeline;

- Gene therapies are novel, complex and difficult to manufacture. We could experience manufacturing problems that result in delays in our development or commercialization programs or otherwise harm our business;

- We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies or technologies that are more advanced or effective than ours;

- We currently rely and expect to continue to rely on third-party manufacturers to produce clinical supply of our product candidates; and

- If we are unable to obtain and maintain patent protection or other necessary rights for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad or our rights under licensed patents is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected;

PART I

Item 1. *Business*

Overview

We are a clinical stage genetic medicines company focused on developing transformative therapies for central nervous system, or CNS, disorders with limited or no approved treatment options. Our vision is to fulfill the promise of gene therapy by developing groundbreaking therapies that transform the lives of patients with CNS diseases. The field of genetic medicine is rapidly expanding and we believe we have a differentiated approach to developing treatments for CNS disorders that enables us to select and advance product candidates with a higher probability of technical and regulatory success. We have entered into a strategic research collaboration with the Trustees of the University of Pennsylvania's, or Penn's, Gene Therapy Program, or GTP, headed by Dr. James Wilson, a leader in the genetic medicines field. We also leverage our close working relationship with Penn's Orphan Disease Center, or ODC, to develop historical and prospective comparable natural history patient profiles for comparison to participants in interventional trials. Through this collaboration we have assembled a strong portfolio of genetic medicine product candidates, for which we retain global rights, including our two lead clinical product candidates: PBGM01 for the treatment of GM1 gangliosidosis, or GM1, and PBFT02 for the treatment of frontotemporal dementia, or FTD; and two clinical stage product candidates for which, in order to reduce operating expenses, we have stopped further clinical development and are exploring strategic alternatives: PBKR03 for the treatment of Krabbe disease and PBML04 for metachromatic leukodystrophy, or MLD. We have two programs in the research stage: PBAL05 for amyotrophic lateral sclerosis, or ALS, and an unnamed program for Huntington's disease. We also have an exploratory research program for Temporal Lobe Epilepsy, or TLE.

We founded Passage Bio with the intent to build a differentiated CNS genetic medicines company delivering transformative therapies to patients by combining our team's experience in rare and neurological disease development, manufacturing and commercialization with the pioneering research expertise of GTP in gene therapy. We are purposefully focusing on rare CNS disorders for which we believe our genetic medicine approach provides distinct technical advantages based on decades of research by GTP. GTP conducts rigorous preclinical studies to identify promising product candidates. Our collaboration provides us with access to cutting edge capabilities and innovation in the field of genetic medicine research, including capsid engineering and next-generation capsid libraries, vector engineering, transgene design and gene therapy modalities, animal disease models and related studies for lead-optimization of product candidates. Further, we believe our team's deep clinical development experience in rare and neurological diseases will enable well planned clinical trials with the potential for efficient advancement to regulatory approval. In addition, we are engaging with key opinion leaders, practitioners and patient advocacy groups in the field of rare CNS disorders who provide strategic input and help inform our clinical development activities. We believe that our ability to execute on the above tenets provides us with product candidates that have an improved profile for clinical development and an enhanced probability of success.

We are focused on developing and commercializing disease-modifying therapies that can have a transformative impact on patients' lives. Utilizing our rigorous selection process, we have assembled a strong portfolio of product candidates for rare, monogenic CNS disorders. Our first product candidate, PBGM01, utilizes a next-generation AAVhu68 capsid to deliver to the brain and peripheral tissues a functional *GLB1* gene encoding lysosomal beta-galactosidase, or β-gal, for GM1. Our second product candidate, PBFT02, utilizes an AAV1 capsid to deliver to the brain a functional *GRN* gene encoding progranulin, or PGRN, for FTD caused by progranulin deficiency, or FTD-GRN. There are currently no approved disease-modifying therapies for these diseases. We believe our clinical product candidates have the potential to provide patients with significantly improved outcomes, given our chosen route of intra cisterna magna, or ICM, administration, the potential for enhanced benefits due to cross-correction of neighboring cells by secreted gene products, and our rigorous capsid and transgene selection process.

Our research collaboration with GTP provides us with access to one of the premier research institutions in the world for the discovery and preclinical development of genetic medicine product candidates and exclusive rights to product candidates for certain CNS disorders. As part of this collaboration, we have exclusive rights to all discovery work and IND-enabling research for product candidates in the CNS indications that we select. In

addition to our two lead clinical product candidates, we have two clinical product candidates for which, in order to reduce operating expenses, we have stopped further clinical development and are exploring strategic alternatives, two ongoing research programs, and eight remaining options available to us to license additional programs from GTP until August 2026. We also have an exploratory research program with GTP in non-rare, non-monogenic, or large, CNS indications, currently focused on TLE, which can be expanded to other large, CNS diseases upon mutual agreement with GTP. Further, we have exclusive rights, subject to certain limitations, to technologies resulting from the discovery program for our products developed with GTP, such as novel capsids, toxicity reduction technologies, delivery, and formulation. We have global commercial rights to all of our current and future product candidates and believe that our approach to developing therapies for life-threatening diseases that are currently underserved presents an opportunity to efficiently advance our product candidates through clinical development, regulatory approval and ultimately to commercialization.

We are led by pioneers and experts with decades of collective experience in genetic medicines and rare disease drug development, manufacturing and commercialization. Dr. Wilson, one of our scientific founders, is recognized as a world leader in research and development in the fields of genetic medicines and rare disease. Dr. Wilson's continuing relationship with our company helps guide our clinical and research programs. We have assembled a team whose members have extensive experience in successfully developing, manufacturing and commercializing genetic medicine and rare disease products.

Our pipeline

We have assembled a strong portfolio of genetic medicine product candidates for rare, monogenic CNS disorders characterized by high unmet medical needs. We intend to further expand our portfolio with genetic medicine product candidates for other CNS disorders, as well as other treatment approaches as technology advances in the field. Our development programs consist of:

**8 additional CNS pipeline license options remain; 3 license options were previously exercised, and rights were subsequently returned to the University of Pennsylvania.*
† Program includes ongoing natural history study of infantile and juvenile GM1 gangliosidosis patients

PBGM01 for the treatment of GM1

We are currently developing PBGM01, which utilizes a proprietary, next-generation AAVhu68 capsid to deliver to the brain and peripheral tissues a functional *GLB1* gene encoding β-galactosidase (or β-gal) for infantile GM1. Infantile GM1 is the most common and severe form of GM1, in which patients have mutations in the *GLB1* gene that produce little or no residual β-gal enzyme activity. β-gal is an enzyme that catalyzes the first step in the natural degradation of GM1 ganglioside as well as other glycan substrates. Reduced β-gal activity results in the accumulation of toxic levels of GM1 ganglioside in neurons throughout the brain, causing rapidly progressive neurodegeneration, with a life expectancy of two to ten years. Currently, there are no disease-modifying therapies approved for the treatment of GM1. Early onset infantile GM1 is characterized by onset in the first 6 months of life, while late onset infantile GM1 is characterized by onset between 6 and 24 months. We believe PBGM01 could provide patients with significantly improved outcomes. In

preclinical studies we observed meaningful transgene expression in both the CNS and in peripheral organs affected in GM1. We are conducting clinical trials using an ICM method of administration, which involves an injection at the craniocervical junction.

We have an active Investigational New Drug application, or IND, from the U.S. Food and Drug Administration, or FDA, and approved clinical trial authorizations, or CTAs, in multiple countries for PBGM01, and we are actively proceeding with our Imagine-1 Trial, an international, multi-center, open-label, single-arm Phase 1/2 clinical trial of PBGM01 in patients with a diagnosis of early and late infantile GM1.

We have completed dosing of the initial four cohorts in our Imagine-1 Trial. This includes a total of eight patients, as follows: Cohort 1 for late infantile GM1 treated with low dose PBGM01, Cohort 2 for late infantile GM1 treated with high dose PBGM01, Cohort 3 for early infantile GM1 treated with low dose PBGM01, and Cohort 4 for early infantile GM1 treated with high dose PBGM01.

In December 2022 and February 2023, we reported interim safety and biomarker data for the first three cohorts of our Imagine-1 trial. The safety data showed that PBGM01 was well tolerated with no serious adverse events and no evidence of dorsal root ganglion toxicity or complications related to the ICM injection. We observed a dose-dependent increase in β-gal activity in the cerebral spinal fluid, or CSF, coupled with a dose-dependent decrease in CSF levels of GM1 ganglioside. We also reported meaningful improvement in a subset of patients across developmental areas in assessments utilizing the Vineland II and Bayley III scales, performed by caregivers and trained healthcare providers, respectively. The data suggests that stage of disease may be a determinant in treatment outcomes.

We expect to report initial safety and biomarker data from patients in Cohort 4 in the middle of 2023.

A key objective of the initial phase of the Imagine-1 trial is to determine the optimal dose for the confirmatory phase of the study. Based on the favorable safety profile of PBGM01 observed to date, the observed dose-response in key biomarkers, such as CSF β-gal activity and GM1 ganglioside levels, and that our preclinical studies showed no safety signals at doses higher than currently being evaluated in the ongoing clinical trial, we plan to treat additional patients in the Imagine-1 trial at higher doses of PBMG01 than the doses of PBGM01 administered to date in Cohorts 1 to 4. Following regulatory review, we expect to dose the first patient at a higher dose of PBGM01 in the second half of 2023.

The FDA has granted Orphan Drug Designation, or ODD, Rare Pediatric Disease Designation, or RPDD, and Fast Track Designation, to PBGM01 for the treatment of GM1. The European Commission has granted Orphan designation and Advanced Therapy Medicinal Product, or ATMP, designation for PBGM01.

PBFT02 for the treatment of FTD-GRN

We are currently developing PBFT02, which utilizes an AAV1 capsid to deliver a functional copy of the granulin gene, or GRN, encoding for human progranulin, or PGRN, for the treatment of frontotemporal dementia caused by progranulin deficiency, or FTD-GRN. FTD-GRN is an inheritable form of FTD in which patients have mutations in the *GRN* gene, causing a deficiency in PGRN. PGRN is a complex and highly conserved protein thought to have multiple roles in cell homeostasis, neurodevelopment, and inflammation. Emerging evidence suggests that PGRN deficiency in FTD and other neurodegenerative disorders may contribute to lysosomal dysfunction. Currently, there are no disease-modifying therapies approved for the treatment of FTD-GRN. Based on findings in preclinical studies, we believe that PBFT02 may provide FTD-GRN patients with significantly improved outcomes. We selected the AAV1 capsid and ICM administration for PBFT02 because this approach led to extensive and robust expression of human PGRN throughout the brain and spinal cord of non-human primates, or NHPs, and due to the higher PGRN levels in CSF using AAV1 as compared with other serotypes tested. ICM administration of AAV1 to NHPs resulted in supraphysiologic CSF levels of human PGRN compared to levels in healthy human subjects' CSF, and in excess of levels achieved in NHPs with AAVhu68 or AAV5.

We have an active IND from the FDA and approved CTAs in multiple countries for PBFT02, which allows us to proceed with our upliFT-D Trial, an international, multi-center, open-label, single-arm Phase 1/2 clinical trial of PBFT02 in patients with a diagnosis of early symptomatic FTD-GRN.

In August 2022, we dosed the first patient in our upliFT-D trial.

We expect to report initial safety and biomarker data from patients in Cohort 1 in the second half of 2023.

The FDA has granted ODD and Fast Track Designation to PBFT02 for the treatment of FTD-GRN and the European Commission granted Orphan designation for PBFT02.

Other Clinical Product Candidates

We have two clinical product candidates, PBKR03 and PBML04, for which, in order to reduce operating expenses, we have stopped further clinical development and are exploring strategic alternatives for these assets.

PBKR03 utilizes a proprietary, next-generation AAVhu68 capsid to deliver to the brain and peripheral tissues a functional *GALC* gene encoding the hydrolytic enzyme galactosylceramidase to treat Krabbe disease. Krabbe disease is an autosomal recessive lysosomal storage disease caused by mutations in the *GALC* gene, which provides instructions for making an enzyme called galactosylceramidase, which breaks down certain fats, including galactosylceramide and psychosine. This results in the accumulation of galactolipids such as psychosine, resulting in widespread death of myelin-producing cells in the CNS and in the peripheral nervous system, or PNS. We have an active IND from the FDA and approved CTAs in multiple countries for PBKR03 to support our GALax-C Trial, an international, multi-center, open-label, single-arm Phase 1/2 clinical trial of PBKR03 in patients with a diagnosis of infantile Krabbe disease. In March 2022, we dosed the first patient in our GALax-C Trial. In November 2022, we announced plans to stop further clinical development of PBKR03 in order to reduce operating expenses, and are exploring strategic alternatives for this asset.

PBML04 utilizes a proprietary, next-generation AAVhu68 capsid to deliver to the brain and peripheral tissues a functional arylsulfatase A gene, or *ARSA*, encoding the ARSA enzyme to treat Metachromatic Leukodystrophy, or MLD. MLD is a rare, autosomal recessive lysosomal storage disease caused by mutations in the *ARSA* gene, resulting in little or no functional activity of the ARSA enzyme, which is essential for the degradation of sphingolipid cerebroside-3-sulfate, or sulfatide. When the ARSA enzyme is lacking, sulfatides accumulate in lysosomal storage deposits in microglia, oligodendrocytes, and Schwann cells, leading to widespread demyelination. Our preclinical data in *ARSA*-/- mice and in NHPs support the ability of PBML04 administration into CSF to result in dose-dependent increases in brain and CSF levels of functional human ARSA enzyme, leading to improved biochemical, histopathological, behavioral, survival endpoints, and with no safety or toxicity signs up to the highest tested dose in NHPs. Preclinical findings were presented by GTP in 2021. In April 2022, we submitted an IND for PBML04 to support clinical development in MLD. On May 20, 2022, the FDA cleared our IND application for PBML04, which supports PBML04-001, an international, multi-center, open-label, single-arm clinical trial of PBML04 in patients with a diagnosis of late onset infantile MLD. In November 2022, we announced plans to stop further clinical development of PBML04 in order to reduce operating expenses, and are exploring strategic alternatives for this asset.

Research Programs

We have two programs in preclinical research stages under our license agreement with Penn: PBAL05 for ALS and, an unnamed program for Huntington's disease. PBAL05 is targeting patients with ALS who have a gain-of-function mutation in the *C9orf72* gene. Our unnamed program is focused on the treatment of Huntington's disease, a repeat expansion disorder. Beyond this portfolio, through our research collaboration with GTP, we also have the option to license programs for eight additional new indications in CNS diseases along with certain rights and licenses to new gene therapy technologies developed by Penn, such as novel capsids, toxicity reduction technologies and delivery and formulation.

We also have an exploratory research program with GTP for larger non-monogenic indications, currently focused on TLE, which can be expanded to other large CNS diseases upon mutual agreement with GTP.

Our Strategy

We are a genetic medicines company focused on developing transformative therapies for CNS disorders with limited or no approved treatment options. Our vision is to fulfill the promise of gene therapy by developing groundbreaking therapies that transform the lives of patients with CNS diseases.

To achieve our vision, we have assembled a world-class team whose members have decades of collective experience in genetic medicines and rare disease drug development and commercialization. We leverage this experience, to develop treatments that improve outcomes for patients with serious, life-threatening CNS diseases. Patients are considered every step of the way, in every decision we make.

Key elements of our strategy include:

- **Focus on underserved indications for which we can have a transformative impact on patients' lives.** We believe that genetic medicine has the potential to have a transformative impact on CNS disorders, and on patients' lives, by providing them with a treatment for life-threatening diseases with limited or no approved treatment options.
- **Rapidly advance our clinical product candidates through clinical development and commercialization.** We leverage our collaboration with GTP, as well as our internal capabilities, to select optimal product candidates for each indication based on extensive preclinical data, including animal data and disease-specific animal models and biomarkers, thus enhancing the probability of clinical success of our product candidates. Our goal is to select candidates that have the potential to address high unmet clinical needs and have transformative therapeutic effects for patients. If our clinical trials are successful, we plan to meet with regulatory authorities to discuss expedited regulatory approval strategies.
- **Advance and expand our pipeline by identifying and developing additional product candidates into the clinic.** We believe our differentiated drug development approach as well as our internal and partnered research capabilities may allow us to address a broad range of CNS disorders, thus expanding our pipeline. Through our collaboration with GTP, we are continuing to develop additional genetic medicine product candidates targeting life-threatening CNS disorders. We have two lead clinical product candidates, two clinical product candidates for which we have stopped further clinical development in order to reduce operating expenses and are exploring strategic alternatives for these assets, and three additional programs advancing through the research or discovery stage. We also have the option to license eight additional CNS indications from GTP until May 2026.
- **Extend existing and establish new relationships with patients and patient advocacy groups.** Patients are at the core of what we do. We have been engaging with them and with their advocacy groups since our inception and have acquired an intimate understanding of how we can positively impact their lives. These relationships deeply inform us as we develop and ultimately seek to commercialize our product candidates. Our relationship with Penn's ODC, which is currently performing a natural history study for GM1 that we are funding, represents an example of our strategy, and has been helping us to engage effectively with patients. We have a collaboration with Invitae to facilitate genetic testing and support early identification of GM1 through Invitae's Detect Lysosomal Storage Disorders, as well as provide clinical trial information to physicians and patients, and have partnered with InformedDNA to offer free genetic counseling and testing for adults who have been diagnosed with FTD.
- **Continue to develop proprietary manufacturing capabilities.** We believe the quality, reliability and scalability of our genetic medicine manufacturing techniques and know-how will be a critical advantage to our long-term success. We have established robust in-house analytical and process development operations to support ongoing and future manufacturing operations. We have also advanced our manufacturing and testing technology platforms; our in-house laboratory is equipped with state-of-the-art analytical capabilities, capable of assay development and validation, clinical product testing, and process and product development to support viral vector manufacturing. We also have the internal manufacturing

and quality expertise to oversee external manufacturing and supply chain operations provided by third party strategic relationships, such as Catalent Maryland, a unit of Catalent Biologics, Inc, or Catalent. We also have access to a manufacturing suite through Catalent where we have successfully produced GMP material for our clinical programs. This facility is capable of producing sufficient supplies to conduct our planned clinical trials and, supply initial commercial launch of our current clinical product candidates, if approved.

- **Selectively enter into new discovery relationships with premier research institutions and expand our existing collaboration.** We will continue to foster our well-established relationship with Penn, and potentially enter into new collaborations to build or advance our pipeline. We will look to nurture our genetic medicine technology capabilities by keeping abreast of advances in next-generation capsid development, promoter selection, transgene design, gene silencing and gene editing, which will help us to engineer optimal product profiles to address life-threating CNS disorders characterized by high unmet medical needs.

Genetic Medicine Background

Each person's genetic material, or genome, consists of deoxyribonucleic acid, or DNA, in sequences of genetic code called genes. The DNA in the human genome contains approximately three billion nucleotide base pairs, and small changes, or mutations, routinely occur in the base pairs. A mutation in a single gene can alter the amount or activity of the protein expressed by the gene, causing deformities and disease. Currently, there are estimated to be over 10,000 diseases caused by a genetic abnormality in a single gene. These are also known as monogenic diseases. Based on research commissioned by us, we believe there are at least 790 rare monogenic CNS diseases, with few currently approved disease modifying treatments for any rare monogenic CNS diseases. In addition, gene therapy can also be applied to correct biological pathways that are not necessarily inherited or associated with one defective gene. This approach aims to reduce the expression of pathological proteins or increase the production of corrective biological targets. This is the basis for the programs that target non-hereditary conditions such as TLE.

The development of molecular therapeutics to modulate human gene expression and correct disease-causing genetic defects had its advent several decades ago, and with advances in science and a deeper understanding of human genetics it has expanded to include a broader range of genetic medicines with the potential to modulate gene expression through additional molecular mechanisms.

These transformative genetic medicines include gene therapy (delivery of an external gene to replace a defective gene), gene silencing (delivery of a DNA or ribonucleic acid, or RNA, based therapeutic that modulates the transcription or translation of an injurious gene product), gene editing (delivery of a DNA or RNA-based therapeutic that corrects the expression of targeted genes) and combinations of these therapeutic modalities. We believe that this expanded molecular biological tool-box will provide new therapeutics with the potential to deliver highly potent and safe interventions across a diverse set of CNS diseases, offering several advantages, including:

- **Potential to treat most diseases of genetic etiology.** Theoretically, it should be possible to design and deliver a genetic medicine to correct the expression of any human protein whose presence, absence or activity causes disease.

- **Potential to target mechanisms that have not been effectively or safely modulated by traditional small molecule or protein-based therapeutics.** The inherent specificity of genetic medicines for unique nucleic acid sequences can provide a high therapeutic index resulting from high potency and the potential to deliver adequate doses while avoiding off-target safety liabilities.

- **Efficient delivery of transformative therapeutics.** Because genetic medicines are designed to deliver a long-standing effect following a single administration, a single dose of these therapeutics has the potential to provide clinical benefits for many years.

Genetic medicines can be designed to mitigate challenges faced by other approaches in the development of therapeutics for the CNS. CNS disorders are among the most devastating in their impact on patients and their families. These disorders are generally life-threatening to patients. There is a significant need for genetic

medicines that can target these disorders. Our initial programs focus on rare, monogenic CNS disorders because they offer a compelling opportunity for the effective application of genetic medicines.

Our Approach

The field of genetic medicine is rapidly expanding and we believe we have developed a differentiated approach to developing treatments for CNS disorders that allows us to select and advance product candidates with a higher probability of technical and regulatory success. Our gene therapy product candidates use AAV, a small, non-pathogenic virus that is genetically engineered to function as a delivery vehicle, or vector. In our current clinical programs, the AAV is administered to a patient to introduce a healthy copy of a mutated gene, or the transgene, to the cells in a process referred to as transduction. Our current approaches use AAVs to deliver either a (i) replacement non-mutant transgene, or (ii) a combination of a microRNA, known as miRNA, to reduce expression of a mutant transgene, and a replacement non-mutant transgene. The components of an AAV gene therapy vector include the therapeutic gene that makes up the DNA payload, or the transgene, the outer viral shell that encloses the DNA payload, or the capsid, and any promotors added to the vector to boost expression of the transgene. The AAV is often described by the serotype, or strain, of the vector. The core tenets of our approach include a rigorous process for selecting product candidates, mitigation of early development risk through relationships with leading researchers and academic institutions, and mitigation of clinical development risk through deep relationships with patient advocacy groups, key opinion leaders and practitioners. Together, these relationships allow us to directly benefit from decades of collective experience, the latest technologies and contemporary perspectives from patients and their experiences.

Rigorous Process for Selecting Product Candidates

In selecting our product candidates, we focus initially on optimizing transduction and expression of transgenes in the indication-specific target tissues. This involves prioritizing the following principles: selection of the route of administration to maximize transgene biodistribution; selection of capsid, transgene and promoter to optimize efficiency of transduction and expression; leveraging biological mechanisms such as cross-correction to maximize availability of transgene product to target cells; and the effective use of biomarkers to assess treatment effects on transduction, transgene expression and on disease pathophysiology.

- **Optimal route of administration:** Identifying the optimal route of administration for AAV gene therapy is critical to achieving safe and effective levels of transgene expression in the targeted location in the CNS. The optimal route of administration for CNS treatments should also leverage the immuno-privileged aspects of the CNS to reduce the potential effects of neutralizing antibodies, or NAbs, on AAV capsids, which are often faced by gene therapy product candidates. We evaluate preclinical studies and other data to decide the preferred route of administration on a program-by-program basis. For our existing clinical product candidates, we believe that ICM administration is the optimal route of administration as compared to other potential delivery mechanisms due to its diffuse delivery distribution, potential for improved biodistribution to the brain and spinal cord and transduction, and lower expected toxicity. Administration through ICM can also reduce the potential impact of NAbs as compared with intravenous administration. We believe that by using ICM we can achieve comparable protein expression at lower dosages than would be required by other administration routes.

- **Capsid, transgene, and promoter selection:** For each of our programs, we conduct rigorous studies to select the capsid, transgene, and promoter to use for our product candidate. We identify the optimal AAV gene therapy for each of our indications depending on the target indication, our goal of CNS and/or PNS transduction, and the target brain regions and cell types. Typically, we compare multiple capsids in NHPs to identify the capsid best suited for each program.

- **Cross-correction:** Our existing clinical product candidates exploit the cross-correction mechanism by which secreted gene product from transduced cells is taken up by non-transduced neurons. We believe this cross-correction mechanism can help overcome the limits of vector biodistribution and CNS transduction inefficiency that are characteristic of other genetic medicine approaches, and ultimately drive clinical benefit.

- **Effective use of biomarkers:** Our development program targets must have measurable, predictive biomarkers to inform early and efficient clinical development decisions. These include pharmacodynamic biomarkers to confirm achievement of target levels of transduction and gene expression, and disease activity and progression biomarkers to confirm downstream effects on the underlying disease pathophysiology.

Mitigation of Early Development Risk of Programs Prior to IND submission

We have a strategic research collaboration with GTP, which is led by our co-founder and Chief Scientific Advisor, Dr. Wilson, and which we believe positions us at the forefront of gene therapy research. This collaboration provides us with access to differentiated discovery technology and expertise that informs the basis of our product candidate selection and subsequent development.

Our strategic research collaboration with GTP provides us with access until August 2026 to one of the premier gene therapy research institutes in the world for the discovery and preclinical development of gene therapy product candidates and exclusive rights to certain CNS disorders, including next-generation AAV capsid technology and vector engineering, and state-of-the art preclinical animal studies, including NHP models. Through GTP's staff, we have access to cutting edge expertise and capabilities in gene therapy research and preclinical development.

Our collaboration with GTP allows us to choose programs that have been or will be validated through extensive testing in preclinical disease models, and once selected, to collaborate with GTP on further preclinical optimization of our product candidate, such as vector choice, transgene construct and route of administration. We believe this collaboration improves our probability of technical and regulatory success in developing product candidates that provide transformative clinical benefits.

Once we select a particular CNS indication for further development, GTP, with our close involvement and oversight, embarks on a rational discovery and development program to design product candidates that may provide improved clinical benefit. We usually evaluate transduction efficiency and biodistribution using multiple different capsids in NHPs to select the capsid best suited for the targeted indication. GTP also works to optimize the delivery method used for each product candidate by balancing delivery, efficacy, safety, host immunity and ease of administration. We believe the translational preclinical characterization provided by GTP, including the use of NHP models for vector screening and toxicology, reduces the early-stage development risk of our product candidates.

Mitigation of Clinical Development Risk through Our Relationship with Penn's ODC

We also have a strong relationship with Penn's ODC. As part of our research collaboration with GTP, we have access to Penn's ODC's insights and capabilities in the study of rare diseases. We leverage our close working relationship with Penn's ODC to develop historical and prospective external data for each disease for use in building comparable patient profiles of participants in interventional trials. Penn's ODC is currently performing a natural history study for GM1 funded by us.

Our Product Candidates

GM1—PBGM01

Overview of GM1

GM1 is a rare and often life-threatening monogenic recessive lysosomal storage disease that results in progressive damage to both the CNS and the peripheral tissues. The infantile form of the disease is characterized by onset in the first two years of life with symptoms including hypotonia (reduced muscle tone), progressive CNS dysfunction leading to deafness, blindness, enlarged liver and spleen, rigidity and progressive skeletal dysplasia that leads to restrictive lung disease and aspiration pneumonia. Early onset infantile GM1, or Type I, is characterized by onset in the first six months of life, while late onset infantile GM1, or Type IIa, is characterized by onset between six and 24 months. The disease rapidly progresses, with a life expectancy of less than two years for early infantile GM1 and five to ten years for late infantile GM1.

GM1 is caused by recessive mutations in the *GLB1* gene, which encodes lysosomal acid β-gal, an enzyme that catalyzes the first step in the natural degradation of GM1 ganglioside as well as other glycan substrates. Reduced β-gal activity results in the accumulation of toxic levels of GM1 ganglioside in neurons throughout the brain, causing rapidly progressing neurodegeneration. GM1 manifests as a continuum of clinical severity, ranging from infants with earlier onset and more severe and rapidly progressive disease to those with later juvenile or adult onset, slower progression and less severe manifestations.

The United States incidence of GM1 has been estimated to be approximately 1 in 100,000 live births, with infantile GM1 representing approximately 62.5% of such cases. No states include GM1 in mandatory infant screening. We engaged a third-party data-analytics firm to conduct an analysis of a variety of de-identified electronic medical records. Based on this analysis, we estimate the incidence of infantile GM1 to be approximately 1.4 in 100,000 live births. Currently, there are no approved disease-modifying therapies available. Supportive treatment options include the use of feeding tubes or ventilators for infants with GM1.

Program selection

We chose GM1 as one of our initial lead programs because it met our criteria for rare, monogenic CNS disorders in which we believe we can develop product candidates with a higher probability of technical and regulatory success that will substantially impact on the lives of severely underserved patients. Several key factors supported the decision to focus on GM1 for AAV gene therapy, as described below.

- *Cross-correction*: Following treatment with PBGM01, we expect that newly synthesized functional β-gal will be secreted by transduced cells and provide a source of secreted proteins that could be taken up by surrounding non-transduced and otherwise enzyme-deficient cells. This cellular cross-correction could therefore lead to enzyme replacement broadly throughout the CNS and peripheral organs.
- *Biomarkers*: There are known biomarkers in GM1 that are measurable and available to assist in drug development.
    - *β-gal activity.* Reduced β-gal activity is a hallmark of GM1 and treatment with PBGM01 is expected to restore this activity. To this end, β-gal activity is being measured in CSF and blood.
    - *Pharmacodynamic biomarkers*. Reduced β-gal activity results in the accumulation of GM1 ganglioside and other glycan substrates in neurons throughout the brain. These substrates may be reduced following treatment with PBGM01 and are being measured in CSF, blood, and urine.
    - *Disease progression biomarkers.* Recent MRI studies of infants with GM1 have shown longitudinal changes in MRI in infants with GM1 consistent with progressive brain atrophy and ventricular enlargement, suggesting that brain MRI would be a useful biomarker to detect and help verify treatment effects on disease pathophysiology.
- *Preclinical validation:* We used the *GLB1* knockout mouse disease model showing clinical, biological and histological manifestations of GM1 in preclinical studies. In these studies, we observed a robust dose-related improvement in both neurological status, enzyme activity, histologic lysosomal storage pathology and survival following treatment with PBGM01.

Product Candidate Development Strategy

We have chosen the earliest and most severe form of GM1 for clinical development for several reasons. Within GM1, infantile GM1 represents the greatest medical need, as early onset GM1 infants often do not survive past two years, and thus are in immediate need of an effective therapy. We expect treatment-related efficacy to be measurable sooner after treatment in this more rapidly progressing form of GM1. Patients with onset forms of GM1 later than infantile, which we define as an onset later than 24 months, are caused by less severe reductions of β-gal enzyme activity and generally demonstrate slower progression and more variable clinical courses, likely requiring larger and longer clinical trials and a broader control group. If our initial clinical trials in infantile GM1 are successful, we intend to explore expansion of the indication with trials in later onset forms of GM1.

Our Product Candidate

We are developing PBGM01 to treat infantile GM1, with a single dose of PBGM01 by ICM administration. PBGM01 utilizes a next-generation AAVhu68 viral vector to deliver modified DNA encoding the β-gal enzyme to a patient's cells. The goal of this vector and delivery approach is to increase levels of the β-gal enzyme in both the CNS and the peripheral tissues. We selected the AAVhu68 capsid and ICM route of administration due to the superior transduction observed in cells of the CNS and peripheral organs, which are both affected in GM1 disease patients. Based on prior capsid comparison studies, the AAVhu68 vector has the potential to provide corrective β-gal enzyme to both the CNS and peripheral tissues, which we believe gives us the potential to treat both the CNS pathologies and the peripheral manifestations observed in GM1 disease.

We believe gene replacement with PBGM01 and consequent wide brain distribution and uptake of the β-gal enzyme has the potential to greatly reduce the accumulation of GM1 gangliosides, reversing neuronal toxicity, thereby restoring developmental potential and improving the quality of life for treated patients. We will evaluate this clinically by assessing the prevention of further developmental regression and restoration of developmental trajectories, as measured by developmental milestones using accepted clinical scales and observer-reported outcomes.

Preclinical studies

The potential for efficacy of PBGM01 is supported by preclinical findings in GLB1 knockout (*GLB1-/-)* mice. This mouse line develops several characteristics that are reminiscent of the neurological presentation of GM1, including a rapid accumulation of GM1 ganglioside in the brain shortly after birth followed by progressive motor abnormalities and a shortened survival. Intracerebroventricular, or ICV, injection of PBGM01 in *GLB1-/-* mice resulted in persistent dose-dependent elevations in β-gal activity in the brain, CSF, serum, and in peripheral organs. Increased β-gal activity was associated with increased phenotypic and histopathological benefits in the *GLB1-/-* mice including the resolution of pre-existing brain lysosomal storage lesions as assessed by lysosomal associated membrane protein 1, or LAMP-1, immunohistochemistry, improved neurological phenotypes in assays of clinical deficits and animals' gait, and increased survival. Preclinical findings were published by GTP in 2020.

NHP Toxicology Study

A 120-day good laboratory practice, or GLP, compliant toxicology study conducted in NHPs assessed the safety, tolerability, biodistribution and excretion profile of PBGM01 following ICM administration of vehicle or one of three dose levels of PBGM01. PBGM01 vector distributed to the CSF and high levels of gene transfer were detected in the brain, spinal cord and dorsal root ganglia, or DRG. The quantity of vector genomes detected in CNS tissues was generally dose-dependent. PBGM01 also reached high levels in peripheral blood and liver. Measurement of transgene expression by β-gal activity in CSF and serum was limited in NHPs by the nature of the assay, which could not distinguish between human and endogenous rhesus β-gal.
β-gal activity in the CSF and serum was detectable in animals from all dose groups 14 days after PBGM01 administration. In the CSF, animals administered the two higher doses displayed dose-dependent increases in β-gal activity to approximately two-fold and four-fold higher than the levels in vehicle-treated controls, respectively.

There were no blood or CSF abnormalities related to PBGM01 administration except for asymptomatic, mild, and transient increases in CSF leukocytes in the majority of animals from all dose groups. PBGM01 was well-tolerated at all doses evaluated and no adverse effects were detected on body weight or clinical, neurological, or behavioral signs. PBGM01 vector DNA was detectable in urine and feces five days post-administration and was undetectable within 60 days. In response to a potential AAV platform risk reported in NHPs we assayed DRG and TRG toxicity after PBGM01 administration. Mild and transient degeneration of DRGs, TRGs, and associated sensory nerve axonopathy were observed in all dose groups; however, these findings were not linked with any clinical or neurological abnormalities in any animals up to 120 days post-dose.

In summary, based on our preclinical studies, we believe that CSF delivery of PBGM01 has the potential to sufficiently increase β-gal levels in both the CNS and in peripheral tissues to overcome intracellular β-gal deficiency in GM1.

Clinical development

Our clinical development plan is to start with trials in infantile GM1, and if successful, explore expansion of the indication with trials in later onset forms of GM1.

We initiated patient dosing in our Imagine-1 trial, a multi-center, open-label, single-arm Phase 1/2 clinical trial of PBGM01 in patients with a diagnosis of early and late infantile GM1 in March 2021. Primary endpoints include safety and efficacy. Efficacy is being evaluated by the assessment of developmental milestones using accepted clinical scales and observer-reported outcomes. Secondary outcomes include serum and CSF β-gal enzyme activity, GM1 ganglioside levels, and disease progression endpoints including evaluations using electroencephalogram, or EEG, and MRI.

The study enrolled both early and late infantile patients in separate, smaller cohorts. Part 1 of the study includes a total of four cohorts of two patients each, with separate dose-escalation cohorts for late onset infantile GM1 patients, defined as onset prior to 24 months in age and after 6 months in age, and early onset infantile GM1, defined as onset prior to 6 months of age. The study is assessing an initial low dose (3.3x10^10 genome copies/gm brain weight) that exceeds the minimum effective dose, or MED, as determined in our preclinical studies, and a 3-fold greater high dose (1.1x10^11 genome copies/gm brain weight). Cohorts 1 and 2 enrolled patients diagnosed with late infantile GM1 and treated them with low dose and high dose PBGM01, respectively, while Cohorts 3 and 4 enrolled patients diagnosed with early infantile GM1 and treated them with low dose and high dose PBGM01, respectively. All patients are treated with an abbreviated course of low dose steroids. To better understand the clinical significance of the peripheral nerve findings in NHPs, we implemented clinical monitoring in our Imagine-1 trial, consisting of both nerve conduction studies and neurological exams focused on sensory and peripheral nerve function. There is a 60-day interval between all subjects dosed within a cohort to allow review of biomarker and safety data before dosing the next subject.

Following the dose-escalation cohorts, each patient population will be enrolled into a confirmatory cohort. Patients will be evaluated over two years for safety and efficacy, followed by an additional 36 months of long-term follow up.

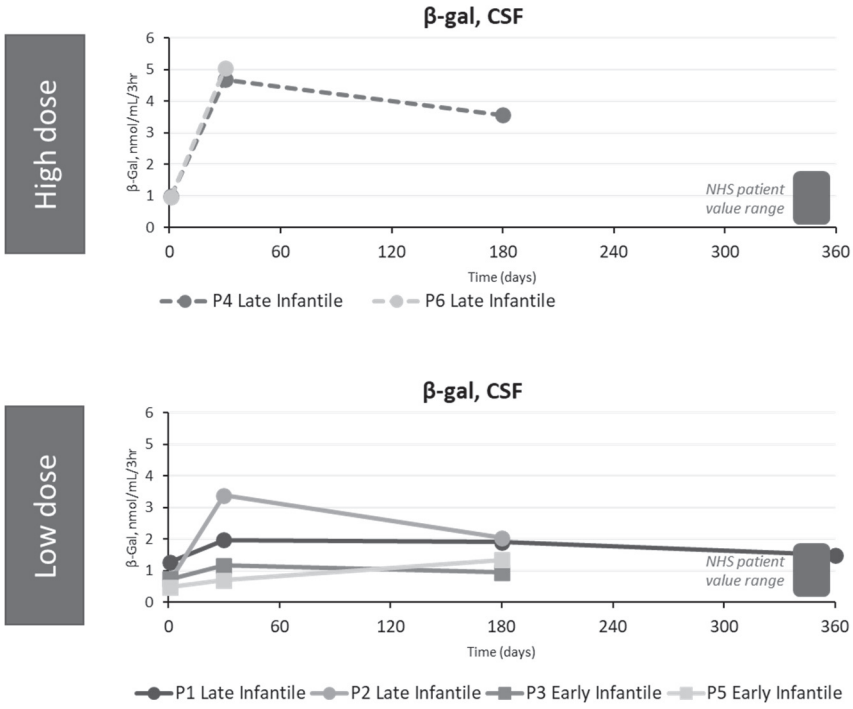
Clinical development results

We completed dosing of the initial four cohorts in our Imagine-1 trial in November 2022. In December 2022 and February 2023, we reported interim safety and biomarker data for the first three cohorts of the trial. The results from the interim assessment are shown below and include clinical data from the first three cohorts with follow-up from three to eighteen months based on data as of December 2022.

PBGM01 was well tolerated, with a positive safety profile, no serious adverse events, or SAEs, and all treatment-related adverse events, or AEs, were mild to moderate in severity. There were no clinically significant changes in liver function requiring intervention and no evidence of peripheral nerve toxicity as measured by nerve conduction studies and neurological exam. There was also a favorable immunological profile with no evidence of an immune response requiring changes to the immunosuppression regimen. As anticipated, moderate levels of Nabs developed to capsid in blood and low levels of NAbs to capsid were also detected in CSF. No antibodies were detected to the transgene product in either the CSF or serum. There were also no complications related to the ICM administration.

The six patients enrolled in Cohorts 1 to 3 ranged from 6 to 31 months of age at the time of PBGM01 administration. Across the first three cohorts, PBGM01 administration resulted in a dose-dependent increase in CSF β-gal activity with the high dose resulting in a 3.6-5.2x increase in CSF β-gal activity relative to baseline, well above levels observed in the Natural History Study being conducted by the University of Pennsylvania ODC. In patient 1, who was observed with the longest follow-up, increased CSF β-gal activity was sustained for 12 months. Sustained β-gal enzyme expression was also observed in blood.

GM1 Cohorts 1-3 Interim CSF β-gal Enzyme Activity



NHS patient value range based on preliminary data from University of Pennsylvania's ODC Natural History Study (NHS) (NCT04041102); Value range (0.3-1.81 nmol/mL/3hr, or nanomole per milliliter per 3 hours)

To assess pharmacodynamic activity in the CNS associated with β-gal activity, GM1 gangliosides levels were measured in the CSF. GM1 gangliosides are hypothesized to mediate CNS manifestation of disease. PBGM01 administration resulted in a dose-dependent decrease in CSF GM1 ganglioside levels for patients in the high dose cohort, showing decreases of up to 75% at six months. GM1 ganglioside levels in the CSF were unchanged following the administration for patients in the low dose cohort.

Clinical assessments include the Bayley III and Vineland II scales, performed by trained healthcare providers and the patients caregivers, respectively. The scales assess the developmental age of the child across a broad range of clinical parameters. The patients treated with PBGM01 exhibited a broad range of developmental age at baseline, as assessed with the Bayley III, as well a wide range of developmental delay, which is determined by the patients chronological age minus their developmental age. Two patients, patients 1 and 5, exhibited developmental delay of 2 and 5.5 months, respectively, which we have characterized as mild-to-moderate delay. The remaining patients exhibited developmental delay ranging from 12 to 24 months, which we have characterized as marked delay.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Diagnosis	Late Onset	Late Onset	Early Onset	Late Onset	Early Onset	Late Onset
Dosing Cohort	Low dose	Low dose	Low dose	High dose	Low dose	High dose
Chronological age at baseline (months)	14	31	15	18	6	17
Developmental age at baseline (Bayley; months)	12	7	0.5	2.5	0.5	5
Developmental delay at baseline (Bayley; months)	2	24	14.5	15.5	5.5	12

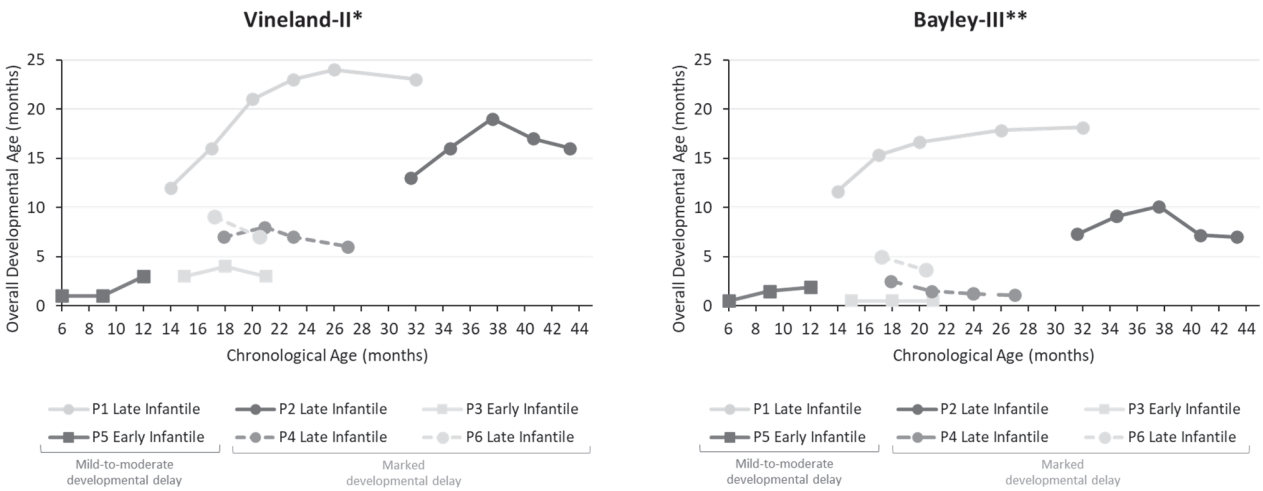
Developmental Delay at Baseline

Mild-moderate delay

Marked delay

Following treatment with PBGM01, we observed that patients with a lower developmental delay at dosing experienced a better clinical response to treatment, regardless of dosage level. On both the Bayley III and the Vineland II, the two patients with mild-to-moderate developmental delay at baseline show improvement in their developmental age over time, which contrasts with the plateau and subsequent regression generally expected based on the natural history of the disease. The remaining patients with more marked developmental delay show stabilization or limited improvement. Based on this data, we believe that milder developmental delay at the time of dosing may be a determinant in treatment outcomes.

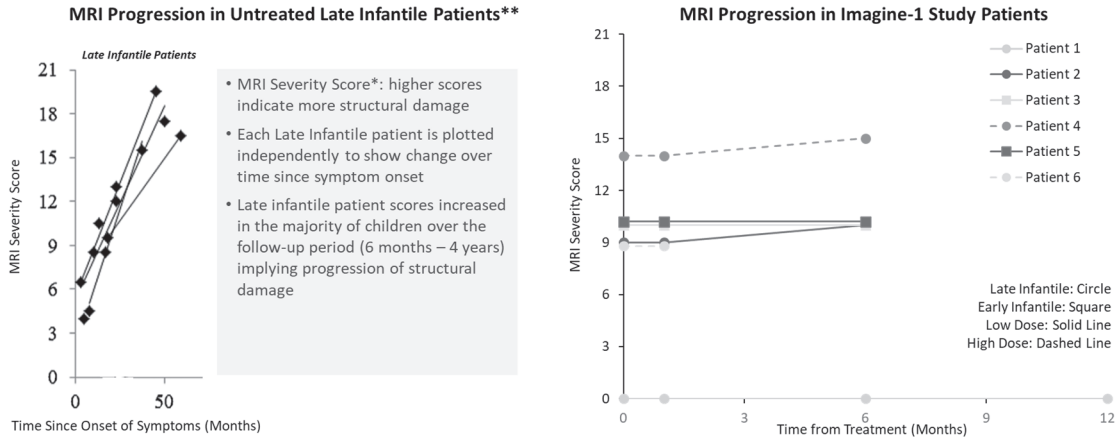
Cohorts 1 – 3 Interim Clinical Results: Vineland-II and Bayley-III



**The Vineland-II is caretaker-assessed.*
***The Bayley-III is based on direct observation by a neurodevelopmental specialist.*

Treatment effects on brain volume and white matter integrity are being assessed using a MRI severity score, a novel scoring metric, for GM1 patients based on baseline and follow-up brain MRI scans. The MRI severity score is based on cerebral and cerebellar atrophy, abnormalities in white matter, and signal abnormalities in the basal ganglia and hippocampi, where higher scores indicate more structural damage. In a natural history study with six late infantile GM1 patients, the MRI severity score increased in the majority of patients over the follow up period of six months to four years, implying progression of structural damage. In contrast, PBGM01 administration was associated with stabilization of the MRI severity score over the follow up period of six to twelve months. While the PBGM01 data is for a shorter period of time than the natural history study data, we believe the initial trend observed, if continued, may be an important indicator of biological activity.

Cohorts 1 – 3 Interim MRI Results: MRI Severity Score



* MRI severity score based on cerebral and cerebellar atrophy, abnormalities in white matter, and signal abnormalities in basal ganglia and hippocampi
** Regier DS, et al. *Am J Med Genet Part A*. 2016;170(3):634-644. Figure adapted to show only late infantile GM1 patients.
MRI, magnetic resonance imaging.

Initial biomarker and safety data from Cohort 4 are expected to be reported in the middle of 2023.

A key objective of the initial phase of the Imagine-1 trial is to determine the optimal dose for the confirmatory phase of the study. Based on the favorable safety profile of PBGM01 to date, the observed dose-response in key biomarkers, such as CSF β-gal activity and GM1 ganglioside levels, and that our preclinical studies showed no safety signals at doses higher than currently being evaluated in the ongoing clinical trial, we plan to treat additional patients in the Imagine-1 trial at higher doses of PBGM01 than the doses of PBGM01 administered to date in cohorts 1 to 4. Following regulatory review, we expect to dose the first patient at a higher dose of PBGM01 in the second half of 2023.

Based on the available data in the Imagine-1 trial to date, we believe that patients with more limited developmental delay at the time of enrollment may have better outcomes. As we consider our pivotal trial design and potential modifications to the ongoing trial, we are revising inclusion criteria to maximize the benefit-risk profile of PBGM01.

As our clinical data matures, we are planning for continued interactions with regulatory authorities to align on design of the confirmatory study and appropriate pathway to submission of a Biologics License Application, or BLA, and regulatory approval for commercialization in the United States and internationally.

Natural History Data

We are currently funding a GM1 natural history study being conducted by Penn's ODC to collect prospective data on clinical disease progression in infantile and juvenile GM1. This data, supplemented with data from retrospective studies, will be used to construct natural history patient profiles for comparison to the profiles of treated participants in our planned Phase 1/2 clinical trial.

Regulatory Designations

The FDA has granted ODD, RPDD, and Fast Track Designation to PBGM01 for the treatment of GM1. The European Commission has granted Orphan designation and Advanced Therapy Medicinal Product, or ATMP, designation for PBGM01.

Clinical Supply

Through our manufacturing partners, we have manufactured the PBGM01 clinical supply and have established a clinical supply chain to support our ongoing clinical trial activities.

FTD—PBFT02

Overview of FTD-GRN

FTD is one of the more common causes of early-onset dementia, occurring with a median age of 55 years. FTD presents as a rapidly progressive clinical syndrome and causes impairment in behavior, language, and executive function. Changes in personal and social conduct occur in early stages of the disease, including loss of inhibition, apathy, social withdrawal, hyperorality and ritualistic compulsive behaviors. These symptoms are severely disabling and may lead to misdiagnosis as a psychological or emotionally based problem, or, in the elderly, be mistaken for withdrawal or eccentricity. FTD progresses to immobility and loss of speech and expression. Survival averages eight years after onset of symptoms.

In approximately 5% to 10% of individuals with FTD, the disease is caused by mutations in the granulin, or *GRN,* gene, causing a deficiency of progranulin. PGRN is a complex and highly conserved protein thought to have multiple roles in cell biology, development and inflammation. Emerging evidence suggests that PGRN's pathogenic contribution to FTD and other neurodegenerative disorders relates to a critical role in lysosomal function.

There are no disease modifying therapies approved for the treatment of FTD. Anti-depressants have been shown to manage some behavioral symptoms. We engaged a third-party data-analytics firm to conduct an analysis of a variety of de-identified electronic medical records. Based on this analysis, we estimate the prevalence of FTD in the United States to be approximately 62,000. The prevalence of FTD due to *GRN* mutation found in literature is 5% to 10%. Accordingly, we estimate the prevalence of FTD-GRN deficiency in the United States to be approximately 3,000 to 6,000.

Program selection

We chose FTD-GRN as one of our initial lead programs because it meets our criteria for rare, monogenic CNS disorders in which we believe we can develop product candidates with a higher probability of technical and regulatory success:

- *Cross-correction:* Following treatment with PBFT02, overexpressing PGRN in a subset of cells in the CNS could provide a source of secreted protein that could be taken up by surrounding cells, resulting in the potential for cross-correction and broad restoration of neuronal lysosomal function across the entire brain.
- *Biomarkers:* There are known biomarkers in FTD-GRN that are measurable and available to assist in drug development.
    - *Pharmacodynamic biomarkers.* PGRN is a secreted protein that can be measured in the CSF and plasma, and it has been shown to be reduced in the CSF of human *GRN* mutation carriers.
    - *Disease progression biomarkers.* We expect to be able to use recent progress in the identification of clinical disease progression biomarkers for FTD, including CSF, neuroimaging and retinal biomarkers, to facilitate clinical development by enabling early detection of treatment effects on disease pathophysiology.
- *Preclinical Validation:* In our preclinical studies in *GRN* knockout mice, or *GRN -/-* mice, ICV administration of PBFT02 resulted in increased levels of PGRN in the CNS and CSF, with resolution of lysosomal storage pathology. ICM administration in NHPs, which do not have the disease phenotype, resulted in robust increases in PGRN levels in CNS and CSF.

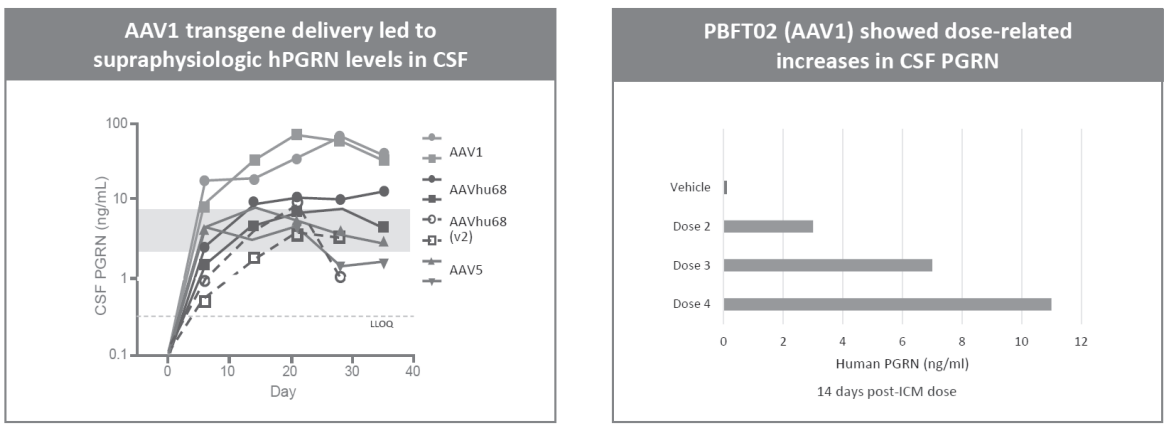
Our Product Candidate

We are developing PBFT02 to treat patients affected with FTD-GRN with a single dose of PBFT02 by ICM administration. PBFT02 is a gene therapy that utilizes an AAV1 viral vector to deliver a modified DNA encoding the *GRN* gene to a patient's cells. The goal of this vector and delivery approach is to provide higher than normal levels of PGRN to the CNS to overcome the progranulin deficiency in *GRN* mutation carriers, who have been observed to have reduced CSF PGRN levels ranging from 30% to 50% of the PGRN levels observed in normal, mutation non-carriers. We selected the AAV1 capsid and ICM administration route due to the widespread and robust expression of the human PGRN transgene observed throughout the brain and spinal cord in NHP studies. Following AAV1 administration in NHP levels of human PGRN in the CSF achieved supraphysiologic levels compared to those measured in healthy human CSF and exceeded PGRN levels observed in NHPs that received AAV5 or AAVhu68 serotypes by greater than 5 times.

Preclinical studies

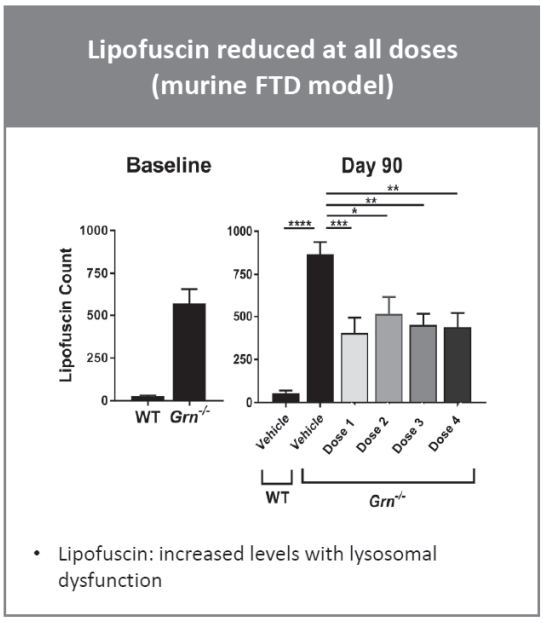
PBFT02 was selected as our development candidate following a study in adult NHPs which evaluated the expression of human PGRN protein in the CSF after ICM administration of four different vector constructs. The AAV1 vector construct produced supraphysiological levels of PGRN and greater than 5 times higher than the other vectors tested, as shown below. ICM AAV1 did not strongly transduce the liver or significantly elevate levels of circulating PGRN, which may reduce the potential for unknown peripheral effects of PGRN. Proof of concept findings were published by GTP in 2020.

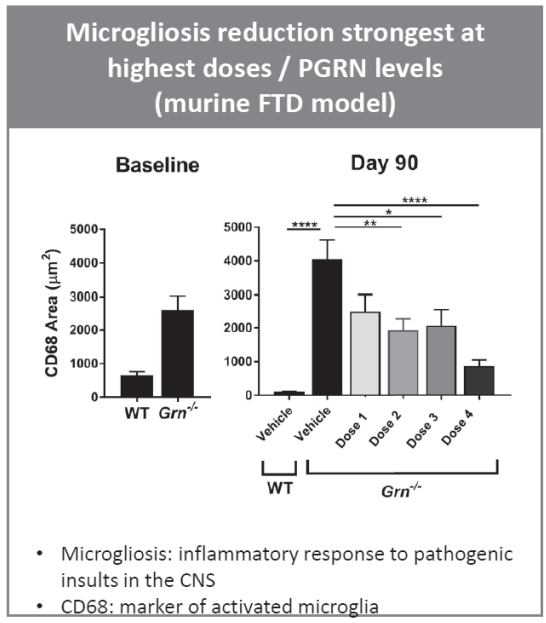
Comparison of Vector Serotypes: Production of Human PGRN-protein in CSF of NHPs following ICM-AAV administration.



Left: Two adult rhesus macaques per treatment received ICM AAV.hPGRN Dose 4, (3.0×10^{13} GC / 3.3×10^{11} GC/g brain) on study day 0[1].
Right: Adult rhesus macaques received ICM PBFT02 (n = 3/dose) or vehicle (n =2) on study day 0.
Shading: Reference range for healthy adult controls' PGRN levels in CSF (n = 61) (Passage Bio data)

The efficacy of the AAV1 vector was assayed in a dose-ranging study in *GRN -/-* mice. PBFT02 was administered via ICV delivery to adult mice at an age when lipofuscin deposition (a marker of lysosomal dysfunction), lysosomal enzyme abnormalities, and neuroinflammation were present in brain regions involved in FTD-GRN pathophysiology. Human PGRN expression in the CSF increased in a dose-dependent manner following PBFT02 administration. Transgene expression led to improvements in histopathologic and enzymatic changes in key brain regions in the mice, including a reduction in the accumulation of lipofuscin and reduced neuroinflammation (as shown in below figure), and elevated lysosomal hexosaminidase activity.





NHP Toxicology Study

A 90-day GLP compliant toxicology study conducted in NHPs assessed the safety, tolerability, biodistribution and excretion profile of PBFT02 following ICM administration at three dose levels. There were no blood or CSF abnormalities related to PBFT02 administration except for asymptomatic, mild, and transient increases in CSF leukocytes in the majority of animals. PBFT02 was well-tolerated at all doses evaluated and no adverse effects were detected on body weight or clinical, neurological, or behavioral signs. Vector distributed to the CSF and high levels of gene transfer were detected in the brain, spinal cord and DRG at Day 90. The quantity of vector genomes detected in CNS tissues was generally dose-dependent. PBFT02 also reached significant concentrations in the peripheral blood, liver and spleen. PBFT02 vector DNA was detectable in urine and feces 5 days post-administration and was undetectable within 60 days.

Human PGRN was detectable in CSF and serum in all animals by 7 to 14 days after PBFT02 administration, peaking between Days 14 to 28. Responses were generally dose dependent and resulted in supraphysiologic PGRN levels after the 2 highest doses. Expression declined by Day 60, correlating with the appearance of antibodies against the human transgene product, which are not expected to develop in haploinsufficient patients with FTD-GRN.

Mild to minimal grade transient degeneration of DRGs and TRGs, and associated sensory nerve axonopathy, were observed in all PBFT02 dose groups. These histopathologic observations were not linked with any clinical or neurological abnormalities in any animals up to 90 days' post-dose. One PBFT02-treated animal exhibited a peripheral nerve conduction impairment in the median nerve, as detected by bilateral reductions in sensory nerve action potential, or SNAP, amplitudes on Day 28 and Day 90, that appeared to be treatment related as severe axon loss and endoneurial fibrosis were detected at necropsy. PBFT02-induced SNAP changes and sensory neuron degeneration were not associated with any clinical or neurological abnormalities in any animals up to 90 days post-dose.

In summary, our preclinical studies demonstrated that CSF delivery of PBFT02 has the potential to safely increase extracellular PGRN levels in the CNS up to supraphysiologic levels and has the potential to improve histopathologic and enzymatic changes in key brain regions associated with FTD.

Clinical development

Our clinical development plan is to treat FTD-GRN with a single dose of PBFT02 via ICM administration, with our initial clinical trial focused on early symptomatic FTD patients who have the *GRN* mutation.

This trial is expected to be a two-cohort dose-escalation trial, with three subjects per cohort, and with a potential for a third higher-dose cohort, if considered necessary based on the results of the first two cohorts. The planned starting dose (3.3x10^10 genome copies/gm brain weight) will exceed the MED in the *GRN* knockout mouse model, with planned escalation to a higher dose (1.1x10^11 genome copies/gm brain weight). The primary endpoint of the trial is to assess safety and tolerability over 60 months. To better understand the clinical significance of the peripheral nerve findings in NHPs, we implemented clinical monitoring in our uplift-D interventional trial, consisting of both nerve conduction studies and neurological exams focused on sensory and peripheral nerve function. Secondary endpoints are to assess change from baseline to 24 months on biomarkers, including CSF and plasma progranulin levels, biomarkers of neurodegeneration and disease progression, and on clinical outcomes as measured by the Clinical Dementia Rating, or CDR, for improving evaluation of patients with frontotemporal lobar degeneration, or FTLD, or CDR®, plus NACC FTLD, and other neurocognitive assessments. Interim analyses are planned for certain biomarkers starting at one month post dosing and for clinical outcomes beginning at one year post dosing. The independent data monitoring committee, or IDMC, will review 30-day biomarker data and safety data for each subject in a cohort. All subjects will be followed for a total of five years to monitor safety and selected biomarker and efficacy measures. All subjects will be evaluated over two years for safety and efficacy, followed by an additional 36 months of long-term follow up.

A scientific advice meeting with MHRA was held in November 2020, providing feedback on our proposed protocol. Feedback was also obtained from other regulatory agencies outside the United States.

In August 2022, we dosed the first patient in our upliFT-D trial.

We expect to report initial safety and biomarker data from patients in Cohort 1 in the second half of 2023.

Depending on the results from the initial cohorts, we plan to obtain input from regulatory agencies on the requirements to submit for regulatory approval for commercialization in the United States and internationally.

Regulatory designations and Clinical Trial Approvals

We have an active IND from the FDA and approved CTAs in multiple countries for PBFT02, which allows us to proceed with our upliFT-D Trial, an international, multi-center, open-label, single-arm Phase 1/2 clinical trial of PBFT02 in patients with a diagnosis of early symptomatic FTD-GRN.

The FDA has granted ODD and Fast Track Designation to PBFT02 for the treatment of FTD-GRN and the European Commission granted Orphan designation for PBFT02.

Clinical Supply

Through our manufacturing partners, we have manufactured the PBFT02 clinical supply to support ongoing clinical trial activities.

Other Research Programs

We have two additional programs in candidate selection or discovery stages of preclinical research, in collaboration with GTP. These include PBAL05 for ALS and our unnamed program for Huntington's disease.

Overview of C9orf72 ALS - PBAL05

C9orf72-mediated Amyotrophic Lateral Sclerosis, or C9orf72 ALS, is an adult-onset, rapidly progressing neurodegenerative disease characterized by dysfunction and death of upper and lower motor neurons leading to progressive weakness, loss of motor function, and death typically within three to five years of disease onset. Most cases of ALS are sporadic with an unknown etiology, but approximately 10% of patients have autosomal

dominantly inherited forms. We are focusing on C9orf72-mediated ALS, since mutations in the *C9orf72* gene are the most common mutation found in ALS patients including both familial (approximately 40% of familial ALS cases) and sporadic ALS cases (approximately 8% of sporadic ALS patients carry C9orf72 mutations), accounting for approximately 11% of all ALS cases. In 2021, the total number of prevalent C9orf72 ALS cases was estimated to be approximately 4,500 worldwide. In these cases, the disease is caused by a hexanucleotide repeat expansion in the first intron of C9orf72. The pathogenic mechanism of C9orf72 mutations is not yet proven, but three potential mechanisms predominate, which are toxic gain of function arising from deposition of transcribed atypical dipepetide repeat proteins, and/or deposition of mutant ribonucleic acid, or RNA, and/or loss of function of endogenous proteins.

Our approach is to use a single AAV vector to deliver a miRNA and a codon-optimized miRNA-resistant C9orf72 transgene combination, to both deplete normal and mutant mRNA within cells with the miRNA and to replace with functional wildtype human transgene. This program is currently at the discovery stage.

Unnamed Research Program

With GTP we have one additional specified research program, to develop a genetic medicine to treat Huntington's disease. This program, initiated in 2021, is currently in the discovery stage. Beyond this portfolio, through our research collaboration with GTP, we also have the option to license programs for eight additional indications.

Exploratory Research Program

We have an exploratory research program with GTP with the goal of developing genetic medicines for non-rare CNS disorders. The program is currently focused on treatment-resistant TLE, and can be expanded to other large CNS diseases upon mutual agreement with GTP.

Manufacturing

Gene therapy manufacturing is a critical factor in the successful development and commercialization of novel genetic medicines, and to that end, we have established internal CMC capabilities to support our vector manufacturing and production platform and we have a relationship with Catalent, a contract development and manufacturing organization, or CDMO, for our initial manufacturing needs.

We utilize a production platform approach with HEK293 mammalian cells as the substrate, triple plasmid transient transfection and single-use fixed-bed iCELLis® bioreactor system for the manufacture of our AAV product candidates. We are using a well-characterized production platform that has been used for both commercial and clinical AAV products and product candidates. We believe our approach will enable rapid development, control of product quality and regulatory compliance.

We have invested significantly in our internal laboratory capabilities and infrastructure to support the manufacturing of our clinical product candidates. Our in-house laboratory is equipped with state-of-the-art analytical and process development capabilities to support and enhance our viral vector manufacturing platform. We have developed the internal technical and scientific capability along with the manufacturing and quality expertise to develop, transfer, and oversee vector production systems externally at commercial scale. We believe our capabilities provide a core strategic advantage and position us to be a leading drug development company to address CNS disorders.

GTP currently provides us with the preclinical and toxicology research-grade vector supplies, while Catalent provides us with the cGMP AAV clinical supplies for our clinical trials. The production process for our two lead clinical stage product candidates, PBGM01 and PBFT02, and for the two clinical stage product candidates for which we have stopped clinical development, PBKR03 and PBML04, has been scaled up to GMP standards at Catalent's facility. Clinical materials for these candidates have been manufactured.

We have a collaboration agreement with Catalent, or the Collaboration Agreement, that gives us access to a cGMP manufacturing suite. Access to cGMP manufacturing capacity gives us the ability to meet production requirements for our current clinical product candidates supporting current and future clinical trials. We also have a development services and clinical supply agreement, or the Manufacturing and Supply Agreement, with Catalent to support clinical scale manufacturing for our gene therapy product candidates.

We entered into a lease to support chemistry, manufacturing and controls laboratory operations for our gene therapy programs, which commenced in March 2021, in the Princeton West Innovation Campus. In 2021, we completed our build out of this new laboratory that is initially focused on state-of-the-art analytical capabilities, assay development and validation, and clinical product testing to support both viral vector manufacturing and clinical development. Since then, we have been able to internalize all major CMC laboratory capabilities, including process development, which will enable late-stage development and commercialization of our gene therapies. We have advanced our manufacturing platform which can be leveraged across our clinical and pre-clinical pipeline through standardization of our manufacturing and analytical technologies.

We believe that our manufacturing capabilities provide us with the advantages of better control of drug development timelines, improved control of vector supply for a portfolio of clinical assets and improved control of product quality through the improvements of the manufacturing platform.

We also anticipate that we will continue to make significant investments to further optimize our manufacturing capabilities and platforms to produce high-quality, cost-effective AAV vectors and we will continue to make investments in process and analytical sciences, internally or with third parties, to evaluate and develop manufacturing process improvements that may increase the productivity and efficiency of our manufacturing platform processes.

Competition

The biotechnology and pharmaceutical industries, including the genetic medicines field, are characterized by rapidly changing technologies, competition and a strong emphasis on intellectual property. We are aware of several companies focused on developing gene therapies in various indications as well as several companies addressing methods for modifying genes and regulating gene expression. We may also face competition from large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions with genetic medicine and other therapeutic approaches.

We consider our most direct competitors with respect to PBGM01 for the treatment of GM1 to be Lysogene, S.A, or Lysogene, which is developing a gene therapy treatment administered via intracisternal magna for early and late infantile GM1. As of February 2022, Lysogene reported having dosed three patients and enrolled a fourth patient in the safety cohort. The National Institutes of Health is conducting a clinical trial for an IV gene therapy treatment for early and late infantile/juvenile GM1 and reported data from ten patients in October 2021. There are also preclinical enzyme replacement therapies in preclinical development.

We consider our most direct competitors with respect to PBFT02 for the treatment of FTD-GRN to be Alector, Inc. (partnered with GlaxoSmithKline), which is enrolling a Phase 3 clinical trial with a humanized anti-human sortilin monoclonal antibody for FTD-GRN, and Prevail Therapeutics Inc. (now part of Eli Lilly & Co), which has initiated a Phase 1/2 clinical trial for a gene therapy treatment for FTD-GRN, and is expected to continue enrolling through 2023. Several other companies, including AviadoBio Ltd, Applied Genetic Technologies Corporation (recently acquired by Syncona Limited), and Orchard Therapeutics plc, are conducting preclinical research using gene therapy approaches to treat FTD-GRN patients. AviadoBio Ltd has reported the planned initiation of a phase 1/2 trial in 2023. Denali Therapeutics Inc. in partnership with Takeda Pharmaceutical Company Limited has a preclinical recombinant progranulin protein under evaluation in addition to their oral EIF2a modulator in a Phase 1 clinical trial. We are also aware of other therapeutic approaches in preclinical development that may target FTD-GRN patients.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any product candidates that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market, if ever. Additionally, new or advanced technologies

developed by our competitors may render our current or future product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

License Agreement

University of Pennsylvania

We have a research, collaboration and licensing agreement, as amended, or the Penn Agreement, with Penn, for research and development collaborations and exclusive license rights to patents for certain products and technologies. Under the Penn Agreement, we have the obligation to fund certain research relating to the preclinical development of selected products in research programs as well as the new exploratory research program in non-rare and/or non-monogenic, or large, CNS indications, initially TLE. We also fund discovery research conducted by Penn through August 2026 and will receive exclusive rights, subject to certain limitations, to technologies resulting from the discovery program for products developed with GTP, such as novel capsids, toxicity reduction technologies and delivery and formulation improvements. Our discovery research funding commitment is $5.0 million a year for five years, with quarterly payments of $1.3 million through June 2026. Under the Penn Agreement we have eight remaining options available to us to commence additional licensed programs for CNS indications until August 2026. If we were to exercise any of these remaining options, we would owe Penn a non-refundable aggregate fee of $1.0 million, with $0.5 million per product indication paid immediately and another $0.5 million fee owed upon a further developmental milestone.

The Penn Agreement requires that we make payments of up to (i) $16.5 million per product candidate for rare, monogenic disorders in aggregate and (ii) $39.0 million per product candidate in the aggregate arising from the exploratory program for large CNS indications, currently TLE and such other mutually agreed upon large CNS indications. Each payment will be due upon the achievement of specific development milestone events by such licensed product for a first indication, reduced development milestone payments for the second and third indications and no development milestone payments for subsequent indications. In addition, on a product-by-product basis, we are obligated to make up to $55.0 million in sales milestone payments on each licensed product based on annual sales of the licensed product in excess of defined thresholds.

Upon successful commercialization of a product using the licensed technology, we are obligated to pay to Penn, on a licensed product-by-licensed product and country-by-country basis, tiered royalties (subject to customary reductions) in the mid-single digits on annual worldwide net sales of such licensed product. In addition, we are obligated to pay to Penn a percentage of sublicensing income, ranging from the mid-single digits to low double digits, for sublicenses under the Penn Agreement. The agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the later of (i) the expiration of the last valid claim of the licensed patent rights that covers the exploitation of such licensed product in such country, and (ii) the expiration of the royalty period. At any time after August 2026, we may terminate the agreement in its entirety, or for a licensed product, for convenience upon 90 days' prior written notice to Penn. Penn may terminate the agreement on an indication-by-indication basis if we fail to meet any diligence event and fail to timely cure such breach, or the agreement in its entirety if we fail to pay the research funding, fail to comply with applicable laws, grant a security interest in any of the licensed patent rights, fail to achieve certain financing obligations, or make certain challenges to the licensed patent rights. Either party may terminate the agreement for the other party's insolvency or material breach that is not cured within a specified period of time. In addition, we will pay Penn a tiered transaction fee ranging from 1-2% of the net proceeds upon certain change of control events.

The Penn Agreement includes an exploratory research collaboration to identify targets and early product candidates in such large CNS indications. The exploratory research program is focused on discovering targets and novel gene therapy candidates for large CNS diseases, currently focused on TLE, and that can be expanded to other large CNS diseases upon mutual agreement. The initial term of the exploratory research program is 3 years, or until August 2024, which term can be extended by mutual agreement. During such term we will have an exclusive right of first negotiation to include additional targets to the exploratory research program in the agreed upon large CNS indications. Under the exploratory research program, we will have the right to further develop and commercialize any gene therapy product candidates specific for those selected targets within TLE (and any future large CNS indications that are mutually agreed upon) that arise from the exploratory research programs on

substantially the same terms of the current Penn Agreement. In November 2022, we agreed with GTP to not continue further advancement of our exploratory research program in AD.

Penn will notify us of any patented manufacturing methods developed by GTP during the specified research term, and we have the option to obtain a non-exclusive license under those patent rights controlled by Penn for our licensed products.

On a CNS indication-by-indication basis, Penn has agreed that GTP will not collaborate with any commercial third party to develop another gene therapy product for the same indication during, or for one year following, its work for us on a given indication and licensed product. Under the licensed Penn patent rights, Penn retains the right to conduct (and to authorize non-commercial third parties to conduct) certain educational, research, clinical and patient care activities.

Under the Penn Agreement, we are obligated to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize at least one licensed product for each of the licensed indications for prophylactic, diagnostic and therapeutic uses in humans. We may satisfy this obligation by achieving, for each licensed product, certain diligence events by a specified achievement date, which dates may be extended under certain circumstances. Pursuant to the agreement, Penn will be responsible for preclinical development activities, including all IND-enabling non-clinical studies and research grade manufacturing, and other collaborative activities set forth in the plan for the funded research, and we will be responsible for regulatory strategy and operations, clinical development, GMP manufacture and commercialization of all licensed products.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary and/or intellectual property protection in the United States and other countries for our current product candidates and future products, as well as our core technologies, including our manufacturing know-how. We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business by seeking, maintaining and defending our intellectual property, whether developed internally or licensed from third parties. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy. Additionally, we intend to rely on regulatory protection afforded through rare drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available.

Currently, our patent protection consists of patent applications that we have in-licensed from Penn under the Penn Agreement for our product candidates in our licensed indications and a patent application that we filed and solely own related to a process for manufacturing our products.

The in-licensed patent applications are directed to new AAV capsids and certain defined variants, to recombinant AAV viruses, or rAAVs, capable of delivering certain genes into human cells to treat monogenic diseases of the CNS, to methods of treating those monogenic diseases with rAAV, as well as certain aspects of our manufacturing capabilities and related technologies. Our in-licensed patent portfolio currently includes:

- a patent family with applications pending in the United States and certain foreign jurisdictions with claims directed to rAAVs having an AAVhu68 capsid. We exclusively licensed the patent family for licensed products within our rare, monogenic field of use indications. Any patents that may issue from applications in this family are expected to expire on February 27, 2038, absent any term adjustments or extensions;
- two patent families with claims directed to an rAAV containing a coding sequence of human β-gal for use in treating GM1. The first patent family includes pending applications in fourteen jurisdictions, including the U.S., Argentina, Brazil, Canada, China, Europe, Israel, Japan, and Korea. Any patents that may issue from applications in this family are expected to expire on September 30, 2039, absent any term adjustments or extensions. The second patent family includes applications pending in sixteen jurisdictions, including the U.S., Argentina, Brazil, Canada, China, Europe, Israel, Japan, and Korea. Any patents that may issue from applications in this family are expected to expire on February 1, 2041, absent any term adjustments or extensions;

- two patent families with claims directed to rAAV for use in treating FTD. The first patent family includes applications pending in fifteen jurisdictions, including the US, Argentina Brazil, Canada, China, Europe, Israel, Japan, and Korea. Any patents that may issue from applications in this family are expected to expire on February 21, 2040, absent any term adjustments or extensions. The second patent family includes applications in Argentina and Taiwan and a pending PCT application. Any patents that may issue from applications in this family are expected to expire on August 26, 2041; and
- one patent family with claims directed to rAAV for use in treating ALS. The patent family includes applications pending in Argentina and Taiwan and a pending PCT application. Any patents that may issue from applications in this family are expected to expire on January 10, 2043, absent any term adjustments or extensions.

We also have options under the Penn Agreement to add additional intellectual property to our existing license, as described in the section "License Agreement".

The term of individual patents may vary based on the countries in which they are obtained. Generally, patents issued from applications filed in the United States are effective for 20 years from the earliest effective non-provisional filing date. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of FDA regulatory review period. The restoration period cannot be longer than five years and the total patent term, including the restoration period, must not exceed 14 years following FDA approval. The duration of patents outside of the United States varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective national filing date.

In addition to patents and patent applications that we license, we rely on trade secrets and know-how to develop and maintain our competitive position. For example, significant aspects of our AAV manufacturing capabilities and gene therapy technology are based upon trade secrets and know-how. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, and obtain and maintain control and/or ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. We also seek to preserve the integrity and confidentiality of our data, trade secrets and know-how, including by implementing measures intended to maintain the physical security of our premises and the physical and electronic security of our information technology systems.

Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to our licensed intellectual property, we cannot be sure that patents will issue with respect to any of the pending patent applications to which we license rights or with respect to any patent applications that we or our licensors may file in the future, nor can we be sure that any of our licensed patents or any patents that may be issued in the future to us or our licensors will be commercially useful in protecting our product candidates and methods of manufacturing the same. Moreover, we may be unable to obtain patent protection for certain of our product candidates generally, as well as with respect to certain indications. See the section entitled "Risk Factors—Risks Related to Our Intellectual Property" for a more comprehensive description of risks related to our intellectual property.

Government Regulation and Product Approval

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 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, such as gene therapy 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. 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 file NDA/BLAs and 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 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 studies to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including Good Laboratory Practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long-term preclinical tests, such as tests of reproductive toxicity and carcinogenicity in animals, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. Clinical trials involve the administration of the investigational biologic to subjects, including 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. subjects 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 regulations or presents an unacceptable risk to the clinical trial subjects. The trial protocol and informed consent information for subjects 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 if it believes that the subjects are subject to unacceptable risk.

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 subjects, the product is tested to assess safety, dosage tolerance, metabolism, pharmacokinetics, pharmacological actions, side effects associated with drug exposure, and to obtain early evidence of a treatment effect if possible. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug or biologic for a particular indication, determine optimal dose and regimen, 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, generally Phase 3 trials are undertaken to obtain additional information about clinical effects and confirm 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 safety and efficacy of the drug or biologic.

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 and distribution of the product may begin in the United States. The BLA must include the results of 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. Under an approved BLA, the applicant is also subject to an annual program fee. These fees typically increase annually. A BLA for a drug that has been designated as an orphan drug is not subject to an application fee, unless the BLA includes an indication for other than a rare disease or condition. The FDA has 60 days from its receipt of a BLA to determine whether the application will be accepted for filing based on the Agency's determination that it is adequately organized and sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals to complete the review of BLAs. Most applications are classified as Standard Review products that are reviewed within ten months of the date the FDA accepts the BLA for filing; applications classified as Priority Review are reviewed within six months of the date the FDA accepts the BLA for filing. A BLA can be classified for Priority Review when the FDA determines the biologic product 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 reviews may be extended by the FDA for three or more additional months to consider certain late-submitted information, or information intended to clarify information already provided in the BLA submission.

The FDA may also refer applications for novel biologic products, or biologic products that present difficult questions of safety or efficacy, to be reviewed by an advisory committee—typically a panel that includes clinicians, statisticians and other experts—for review, evaluation, and a recommendation as to whether the BLA should be approved. The FDA is not bound by the recommendation of an advisory committee, but 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 cGMPs is satisfactory and the BLA contains data that provide substantial evidence that the biologic is safe, pure, potent and effective in the claimed indication.

After the FDA evaluates the BLA and completes any clinical and manufacturing site inspections, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the BLA submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application for approval. 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 and distribution 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 to patients. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure a product's safe use, or ETASU. An ETASU can include, but is not limited to, special training or certification for prescribing or dispensing the product, dispensing the product only under certain circumstances, special monitoring, and the use of patient-specific registries. The requirement for a REMS can materially affect the potential market and profitability of the product. Moreover, the FDA 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 BLA, including changes in indications, product labeling, 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.

Additional Standard for Gene Therapy Products

In addition to the regulations discussed above, there are a number of additional standards that apply to clinical trials involving the use of gene therapy. FDA has issued various guidance documents regarding gene therapies, which outline additional factors that FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical assessment of gene therapies; the CMC information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. For instance, FDA usually recommends that sponsors observe all surviving subjects who receive treatment using gene therapies that are based on adeno-associated virus vectors in clinical trials for potential gene therapy-related delayed adverse events for a minimum 5-year period. FDA does not require the long-term tracking to be complete prior to its review of the BLA.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant Orphan Drug Designation to biological products intended to treat a rare disease or condition—generally a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a product available in the United States for such disease or condition will be recovered from sales of the product. Orphan Drug Designation must be requested before submitting a BLA. After the FDA grants Orphan Drug Designation, the identity of the biological product and its potential orphan disease 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 in the approved indication. For large molecule drugs, including gene therapies, sameness is determined based on the principal molecular structural features of a product. As applied to gene therapies, the FDA has recently issued final guidance in which it stated it generally intends to consider certain key features, such as the transgenes expressed by the gene therapy and the vectors used to deliver the transgene, to be principal molecular structural features. With regard to vectors, the FDA generally intends to consider whether two vectors from the same viral class are the same or different on a case-by-case basis. The FDA does not intend to consider minor differences between transgenes and vectors to be different principal molecular structural features. When two gene therapy products express the same transgene and have or use the same vector, determining whether two gene therapies are the same drug may also depend on additional features of the final gene therapy product, such as regulatory elements and the cell type that is transduced (for genetically modified cells). In such cases, the FDA generally intends to determine whether two gene therapy products are different on a case-by-case basis. During the seven-year marketing 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 indication, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. A product can be considered 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, the 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 the 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, the FDA may designate a product in development as a product for a rare pediatric disease.

To receive a rare pediatric disease priority review voucher, a sponsor must notify the FDA, upon submission of the NDA or BLA, of its intent to request a voucher. If the FDA determines that the NDA or BLA is a rare pediatric disease product application, and if the NDA or BLA is approved, the FDA will award the sponsor of the NDA or BLA a voucher upon approval of the NDA or BLA. The FDA may revoke a rare pediatric disease priority review voucher if the product for which it was awarded is not marketed in the U.S. within 365 days of the product's approval. The voucher, which is transferable to another sponsor, may be submitted with a subsequent NDA or BLA and entitles the holder to priority review of the accompanying NDA or BLA. The sponsor submitting the priority review voucher must notify the 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. The FDA must take action on an NDA or BLA under priority review within six months of receipt of the NDA or BLA.

On December 27, 2020, the Rare Pediatric Disease Priority Review Voucher program was reauthorized as part of the Consolidated Appropriations Act, 2021 allowing a product that is designated as a product for a rare pediatric disease prior to September 30, 2024 to be eligible to receive a rare pediatric disease priority review voucher upon approval of a qualifying NDA or BLA prior to September 30, 2026. It is unclear whether this program will continue to be reauthorized beyond the current sunset date in September 2024.

Fast Track Designation and Priority Review

The FDA is required to facilitate the development, and expedite the review, of drugs 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. Fast track Designation may be granted for products that are intended to treat a serious or life-threatening disease or condition for which there is no effective treatment and preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. Fast track Designation applies to both the product and the specific indication for which it is being studied. Any product submitted to the FDA for marketing, including under a fast track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review.

Priority review may be granted for products that are intended to treat a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness compared to available therapies. The FDA will attempt to direct additional resources to the evaluation of an application designated for priority review in an effort to facilitate the review.

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 on the website www.clinicaltrials.gov. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of a clinical trial are then made public as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of clinical 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 clinical development programs as well as clinical trial design.

Pediatric Information

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

orphan product designation except a product with a new active ingredient that is a molecularly targeted cancer product intended for the treatment of an adult cancer and directed at a molecular target determined by FDA to be 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, 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 biologics 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 within the United 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 lot manufacturing history 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 allowing the manufacturer to release the lots for distribution. 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 a BLA, 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.

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 studies, and a clinical trial or trials, unless the Secretary of Health and Human Services waives a required element. A biosimilar product may be deemed interchangeable with a previously approved product if it meets the higher hurdle of demonstrating that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. The first biosimilar product was approved by the FDA in 2015, and the first interchangeable product was approved in 2021.

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

Post-Approval Requirements

Once a BLA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of biologics, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and

promotional activities involving the Internet. Biologics may be marketed only for the approved indications and in accordance with the provisions of the approved labeling.

Adverse event reporting and submission of periodic safety summary reports are 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 a biologic product's 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 required regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

Other U.S. Healthcare Laws and Compliance Requirements

In the United States, biotechnology company 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 & Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General and the Office for Civil Rights), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. The laws biotechnology companies may have to comply with include the anti-fraud and abuse provisions of the Social Security Act, the federal false claims laws, the privacy and security provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended, as applicable.

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, recommending 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/or 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. Practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor. In addition, the statutory exceptions and regulatory safe harbors are subject to change.

Additionally, the intent standard under the Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the 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.

Federal false claims laws, including the federal civil False Claims Act, prohibit, 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. In addition, manufacturers can be held liable under the civil False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, 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 and purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes.

HIPAA created additional 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. Similar to the Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

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.

Data privacy and security regulations by both the federal government and the states in which business is conducted may also be applicable. 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. HIPAA requires covered entities to limit the use and disclosure of protected health information to specifically authorized situations, and requires covered entities to implement security measures to protect health information that they maintain in electronic form. Among other things, HITECH made HIPAA's 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) report annually to CMS information related to certain payments or other transfers of value made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), physician assistants, certain types of advanced practice 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.

Commercial distribution of products requires compliance 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. In addition, 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. Certain local jurisdictions also require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. Sales and marketing activities are also potentially subject to federal and state consumer protection and unfair competition laws.

Violation of any of the federal and state healthcare laws described above or any other governmental regulations may result in penalties, including without limitation, significant civil, criminal and/or administrative penalties, damages, fines, disgorgement, exclusion from participation in government programs, such as Medicare and Medicaid, imprisonment, injunctions, private "qui tam" actions brought by individual whistleblowers in the name of the government, refusal to enter into government contracts, oversight monitoring, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which regulatory approval is obtained. In the United States and markets in other countries, sales of any products for which regulatory approval is received 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. Expensive pharmaco-economic studies may need to be conducted in order to demonstrate the medical necessity and cost-effectiveness of product candidates, in addition to the costs required to obtain the FDA approvals. 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 the maintenance of price levels sufficient to realize an appropriate return on 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 regulatory approval is received for commercial sale may suffer if the government and other third-party payors fail to provide coverage and adequate reimbursement. In addition, emphasis on managed care in the United States has increased and is expected to 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 regulatory approval is received, 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. Healthcare reform proposals recently culminated in the enactment of the Inflation Reduction Act, or IRA, which will eliminate, beginning in 2025, the coverage gap under Medicare Part D by significantly lowering the enrollee 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 will also allow HHS to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D (excluding drugs and biologics that are designated and approved for only one rare disease or condition), although only high-expenditure single-source biologics that have been approved for at least 11 years (7 years for drugs) 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 2022 for Medicare Part D and January 2023 for Medicare Part B, the IRA will also penalize drug manufacturers that increase prices of Medicare Part D and Part B drugs at a rate greater than the rate of inflation. It is unclear to what extent other statutory, regulatory, and administrative initiatives will be enacted and implemented in the future.

Employees and Human Capital Resources

As of December 31, 2022, we had 85 full-time employees. From time to time, we also retain independent contractors to support our organization. Of these employees, 26 held Ph.D., Pharm.D. or M.D. degrees, and 57 were engaged in research, development and technical operations. All of our employees are based in the United States. None of our employees are represented by a labor union or covered by collective bargaining agreements, and we believe our relationship with our employees is good.

Our Mission and Our Employees

At Passage Bio, our mission is to discover and develop transformative therapies for CNS disorders with limited or no approved treatment options, while also building strong relationships with the communities we serve. We embrace collaboration, discipline and efficiency, while welcoming fresh ideas and stimulating personal development. We align our core values with our mission statement, which is outlined below:

- Put patients first
    - We place the health and safety of our patients at the center of every decision we make
    - We value the voice of our patient communities; we listen and we learn
    - We are driven to improve patients' lives; they are relying on us

- Committ to Excellence
    - We apply leading-edge science and technology to develop gene therapies for our patients
    - We strive to be the best in everything we do
    - We embrace diversity and inclusion as essential to the success of our company
    - We have an unrelenting focus on quality

- Make and impact
    - We act with a sense of urgency; patients are waiting
    - We are nimble and adaptable in driving toward our goals
    - We approach every day with courage and tenacity

- Act with integrity
    - We communicate openly, honestly and respectfully with each other
    - We make decisions based on what's right
    - We are accountable for our actions

    - We care about our community and strive to be good citizens

- Suceed together
    - We're all part of the solution and help each other be successful
    - We innovate by challenging the status quo, taking appropriate risk and encouraging diversity of thought
    - We value and foster collaboration, both internally and with our external partners
    - We work hard and find ways to make it fun

Our Commitment to Diversity, Equity and Inclusion

We are committed to creating and maintaining a diverse, equitable and inclusive workplace where all of our employees can thrive in an environment that values differences, provides equal opportunities and embraces different backgrounds and perspectives. We treat all individuals with respect and dignity and provide all of our employees with fair treatment based on merit. By embracing diversity and inclusion, we create an organization committed to working together to develop innovative solutions in support of our mission. Our core values include a commitment to diversity, equity, and inclusion, and we have embraced them as integral parts of our business strategy.

Our Compensation and Benefits

We view our employees as one of our most valuable assets in serving our mission. We compete in the highly competitive biotechnology industry, and attracting, retaining and developing a diverse group of talented employees is crucial to our strategy and our ability to compete effectively. We are committed to the development and retention of our workforce to support our research, clinical operations, manufacturing and regulatory efforts. There currently is a shortage of skilled individuals with substantial experience discovering, developing and manufacturing genetic medicines, which is likely to continue. As a result, competition for these individuals is intense and the turnover rate can be high. We face substantial competition among numerous companies and academic institutions for individuals with these skills.

Given the highly competitive nature of our industry and the importance of recruitment and retention to our success, we strive to provide our employees with what we believe is a very competitive and comprehensive total rewards package of compensation, benefits and services. This package includes at or above-market pay, healthcare benefits for employees and family members, life insurance benefits, short and long-term disability benefits, generous paid time off benefits, parental leave, bereavement leave, flexible work schedules, a 5% employer match of employee contributions to our sponsored retirement plans, and an annual stipend for employees to spend on professional development. Additionally, we also offer every full-time employee the benefit of equity ownership in our Company through our equity plans.

Facilities

Our principal executive office is located in Philadelphia, Pennsylvania, where we lease a total of approximately 37,000 square feet of office space, which commenced in February 2021 and will expire in December 2031, subject to our option to extend the term of the lease by up to two additional five-year terms.

We also lease approximately 62,000 square feet of laboratory space at the Princeton West Innovation Campus in Hopewell, New Jersey. This lease has a 15-year term from the lease commencement date of March 2021. We have the option to extend the term of the lease by up to two additional five-year terms.

Legal Proceedings

From time to time, we may be involved in legal proceedings arising in the ordinary course of our business. We are not presently a party to any legal proceedings that, in the opinion of management, would have a material adverse effect on 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.

Corporate Information

We were incorporated under the laws of the State of Delaware in July 2017 under the name Passage Bio, Inc. Our principal executive office is located at Two Commerce Square, 2005 Market Street, 39th Floor, Philadelphia, PA, 19103, and our telephone number is (267) 866-0311. Our website address is www.passagebio.com. The information contained on, or that can be accessed through, our website is not part of, and is not incorporated by reference into, this prospectus.

Available Information

We file annual, quarterly and current reports, proxy statements and other documents with the Securities and Exchange Commission, or SEC, under the Securities Exchange Act of 1934, as amended, or Exchange Act. The SEC maintains an Internet website that contains reports, proxy and information statements, and other information regarding issuers, including us, that file electronically with the SEC. The public can obtain any documents that we file with the SEC at www.sec.gov. Copies of each of our filings with the SEC can also be viewed and downloaded free of charge at our website, https://investors.passagebio.com/, after the reports and amendments are electronically filed with or furnished to the SEC.

Item 1A. ***Risk Factors***

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before making your decision to invest in shares of our common stock, you should carefully consider the risks and uncertainties described below, together with the other information contained in this annual report, including our financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations". 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. We cannot assure you that any of the events discussed below will not occur. These events could have a material and adverse impact on our business, financial condition, results of operations and prospects. If that were to happen, the trading price of our common stock could decline, and you could lose all or part of your investment.

Risks Related to Our Financial Position and Need for Additional Capital

We are a clinical stage genetic medicines company with a history of operating losses, and we may not achieve or sustain profitability. We anticipate that we will continue to incur losses for the foreseeable future. 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 genetic medicines company with a limited operating history on which to base your investment decision. Biotechnology product development is a highly speculative undertaking and involves a substantial degree of risk. Our operations to date have been limited primarily to staffing our company, business planning, raising capital, entering into collaboration and vendor agreements for conducting preclinical research and clinical development activities for our product candidates, and performing clinical development activites and manufacturing clinical supply. All of our product candidates are in the clinical development stage, have been stopped from further clinical development in order to reduce operating expenditures, or are in the preclinical or discovery stage. We have no products approved for commercial sale and have not generated any revenue from commercial product sales, and we will continue to incur significant research and development and other expenses related to our clinical development and ongoing operations. We have funded our operations to date through proceeds from sales of our convertible preferred stock, and public offerings, and do not expect to receive revenue for many years, if ever.

We have incurred net losses since our inception in 2017. We incurred net losses of $136.1 million and $185.4 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $492.4 million. Substantially all of our operating losses have resulted from expenses incurred in connection with our research and development programs, acquiring the rights to our product candidates, and from general and administrative expenses associated with our operations. We expect to continue to incur significant expenses and operating losses over the next several years and for the foreseeable future as we intend to continue to conduct research and development, clinical testing, regulatory compliance activities, manufacturing activities, and, if any of our product candidates is approved, sales and marketing activities that, together with anticipated general and administrative expenses, will likely result in us incurring significant losses for the foreseeable future. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital.

We expect that it will be several years, if ever, before we have a commercialized product. We anticipate that our expenses will increase substantially if, and as, we:

- our product candidates advance from the preclinical or discovery stage to the clinical development stage;
- our clinical product candidates advance into later stage clinical development;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- hire additional clinical, quality control, regulatory, manufacturing, scientific and administrative personnel;
- expand our operational, financial and management systems and increase personnel, including personnel to support our clinical development, manufacturing and commercialization efforts and our operations as a public company;

- expand or build our internal manufacturing capabilities;
- maintain, expand and protect our intellectual property portfolio; and
- incur additional legal, accounting or other expenses in operating our business, including the additional costs associated with operating as a public company.

In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We are in the process of transitioning rapidly from a small start-up company with a focus on hiring employees, establishing key collaborations and financing to a more fully-integrated company that is capable of supporting clinical development, manufacturing and commercial activities. We may not be successful in such a transition.

We have never generated revenue from product sales and may never achieve or maintain profitability.

We have no products approved for commercial sale and have not generated any revenue from commercial product sales. To become and remain profitable, we must develop and eventually commercialize product candidates with significant market potential, which will require us to be successful in a range of challenging activities. These activities can include completing preclinical studies and initiating and completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products that are approved and satisfying any post marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability.

Even 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 our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment.

We will need to raise additional funding before we can expect to become profitable from any potential future sales of our products. This additional financing may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit, or terminate our product development efforts or other operations.

We will require substantial future capital in order to complete planned and future preclinical and clinical development for our portfolio of product candidates and potentially commercialize these product candidates, if approved. If our product portfolio progresses into later stage clinical trials, or our current preclinical product candidates progress into the clinical trial stage, we expect our spending levels to significantly increase in connection with our continued clinical trial activites and production of our clinical product candidates supply. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on acceptable terms, we would be forced to delay, reduce or eliminate certain of our licensing activities, our research and development programs or other operations.

Our operations have consumed significant amounts of cash since inception. As of December 31, 2022, our cash, cash equivalents and marketable securities were $189.6 million. We expect that our existing cash, cash equivalents and marketable securities will enable us to fund our operating expenses and capital expenditure requirements into the first half of 2025. However, we have based this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect.

Our future capital requirements will depend on many factors, including:

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

Accordingly, we will need to continue to rely on additional financing to achieve our business objectives, which may not be available to us on acceptable terms, or at all. We may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. If adequate funds are not available to us on a timely basis or on terms acceptable to us, we may be required to delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more product candidates or discovery stage programs or delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize any product candidates, if approved.

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 offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or securities convertible into equity, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. 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, selling or licensing our assets, 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. If we are unable to raise additional funds through equity or debt financings when needed or on terms acceptable to us, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to Product Development and Regulatory Approval

We are early in our development efforts. Our business is dependent on our ability to advance our current and future product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them. If we are unable, or experience significant delays in doing so, our business will be materially harmed.

We are early in our clinical development efforts and our clinical product candidates are in early phase clinical trials. Additionally, we have a portfolio of programs that are in different stages of preclinical development and some may never advance to clinical stage development. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. We currently generate no revenue from sales of any product and we may never be able to develop or commercialize a marketable product.

Each of our programs and product candidates will require additional preclinical and/or clinical development, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, capacity and expertise, building a commercial organization or successfully outsourcing commercialization, substantial investment and significant marketing efforts before we generate any revenue from product sales. Our product candidates must be authorized for marketing by the FDA, or certain other ex-U.S. regulatory agencies before we may commercialize our product candidates.

The clinical and commercial success of our product candidates will depend on several factors, including the following:

- timely and successful completion of preclinical studies, including toxicology studies, biodistribution studies, biocompatibility studies and minimally efficacious dose studies in animals, where applicable;
- effective INDs or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for our product candidates;
- successful enrollment and completion of clinical trials, including under the international current Good Clinical Practices, or cGCPs, and current Good Laboratory Practices, or GLPs;
- positive results from our future clinical programs that support a finding of safety and effectiveness and an acceptable risk-benefit profile of our product candidates in the intended populations;
- receipt of marketing approvals from applicable regulatory authorities;
- establishment of arrangements with third-party manufacturers or our own facilities for clinical supply and, where applicable, commercial manufacturing capabilities;
- establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates;
- commercial launch of our product candidates, if approved, whether alone or in collaboration with others;
- acceptance of the benefits and use of our product candidates, including method of administration, if and when approved, by patients, the medical community and third-party payors;
- effective competition with other therapies;
- establishment and maintenance of healthcare coverage and adequate reimbursement and patients' willingness to pay out-of-pocket in the absence of such coverage and adequate reimbursement;
- establishment of a physician training system and network for administration of our product candidates by administration into the ICM;
- enforcement and defense of intellectual property rights and claims; and
- maintenance of a continued acceptable safety, tolerability and efficacy profile of our product candidates following approval.

If we do not succeed in 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. If we are unable to advance our product candidates to clinical development, obtain regulatory approval and ultimately commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

Preclinical and clinical development involve a lengthy and expensive process with an uncertain outcome. We may incur additional expenses or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our current product candidates or any future product candidates.

All of our product candidates are in clinical or preclinical development and their risk of failure is high. We currently rely exclusively on GTP for our preclinical and IND-enabling studies. It is impossible to predict when or if any of our product candidates will receive regulatory approval. To obtain the requisite regulatory approvals to commercialize any product candidates, we must demonstrate through extensive preclinical studies and lengthy, complex and expensive clinical trials that our product candidates are safe and effective in humans. For example, our IND for PBGM01 for the treatment of GM1 was initially placed on clinical hold. Even though the FDA removed the clinical hold on the IND for PBGM01, other future product candidates may be subject to clinical holds in the future. Clinical testing can take many years to complete, and its outcome is inherently uncertain. We will rely on CROs for the clinical development of our clinical product candidates. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials or early cohorts of our clinical trials of our product candidates, including early biomarker data, may not be predictive of the results of later-stage clinical trials or later cohorts of our clinical trials. Early clinical trials and in particular initial cohorts of early clinical trials often enroll significantly fewer patients than later stage clinical trials or later cohorts of the same clinical trial and may not be as predictive as larger trials. We may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful or come to agreement on other aspects of clinical trial design. Moreover, a clinical trial can fail at any stage of testing. Differences in trial design between early-stage clinical trials and later-stage clinical trials make it difficult to extrapolate the results of earlier clinical trials to later clinical trials. Moreover, clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval of their products. A number of companies in the biotechnology industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or to unfavorable safety profiles, notwithstanding promising results in earlier trials. There is typically a high rate of failure of product candidates proceeding through clinical trials. Most product candidates that commence clinical trials are never approved as products and there can be no assurance that any of our future clinical trials will ultimately be successful or support clinical development of our current or any of our future product candidates.

We or our collaborators may experience delays in initiating or completing clinical trials. We or our collaborators also may experience numerous unforeseen events during, or as a result of, any future clinical trials that we could conduct that could delay or prevent our ability to receive marketing approval or commercialize our clinical product candidates or any future product candidates, including:

- regulators, such as the FDA, may place our clinical trials on clinical hold; for example, the FDA placed our trial of PBGM01 for the treatment of GM1 on clinical hold from July 2020 to December 2020;
- institutional review boards, or IRBs, the FDA or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective CROs the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trial sites deviating from trial protocol or dropping out of a trial;
- novel therapies, such as gene therapies with less well-characterized safety profiles, may require slower or more staggered early clinical trial enrollment to adequately assess safety data;
- clinical trials of any product candidates may fail to show safety or efficacy, produce negative or inconclusive results and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs;
- the number of subjects required for clinical trials of any product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or subjects may drop out of these clinical trials or fail to return for post-treatment follow up at a higher rate than we anticipate;
- 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, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;

- we may elect to, or regulators, IRBs, or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants in our trials are being exposed to unacceptable health risks;
- the related expenses of clinical trials of any of our product candidates may be greater than we anticipate;
- the quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be inadequate to initiate or complete a given clinical trial;
- our inability to manufacture sufficient quantities of our product candidates for use in clinical trials;
- reports from clinical testing of other therapies may raise safety or efficacy concerns about our product candidates;
- our failure to establish an appropriate safety profile for a product candidate based on clinical or preclinical data for such product candidate as well as data emerging from other molecules in the same class as our product candidate; and
- the FDA or ex-U.S. regulatory agencies may require us to submit additional data such as long-term toxicology studies, or impose other requirements before permitting us to initiate a clinical trial.

Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors including the size and nature of the patient population, the number and location of clinical sites we enroll, the proximity of patients to clinical sites, the eligibility and exclusion criteria for the trial, the design of the clinical trial, the inability to obtain and maintain patient consents, the risk that enrolled participants will drop out before completion, competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs or therapeutic biologics that may be approved for the indications being investigated by us. Furthermore, we expect to rely on our collaborators, CROs and clinical trial sites to ensure the proper and timely conduct of our future clinical trials, including the patient enrollment process, and we have limited influence over their performance. Additionally, we could encounter delays if treating physicians encounter unresolved ethical issues associated with enrolling patients in future clinical trials of our product candidates in lieu of prescribing existing treatments that have established safety and efficacy profiles. For example, treating physicians with eligible patients for our FTD trial may instead elect to use alternative treatment approaches from our competitors, if such competitors are to receive regulatory approval in advance of our program, in lieu of enrolling in our clinical trial.

We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs of the institutions in which such trials are being conducted, or the FDA or other regulatory authorities, or if a clinical trial is recommended for suspension or termination by the Independent Data Monitoring Committee for such trial. A suspension or termination may be imposed due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product or treatment, failure to establish or achieve clinically meaningful trial endpoints, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Clinical studies may also be delayed or terminated as a result of ambiguous or negative interim results. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates. Further, the FDA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials.

Our product development expenses will increase if we experience delays in clinical testing or marketing approvals. We do not know whether any of our clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates and may allow our competitors to bring products to market before we do, potentially impairing our ability to successfully commercialize our product candidates and harming our business and results of operations. Any delays in our clinical development programs may harm our business, financial condition and results of operations significantly.

Success in early preclinical studies or clinical trials may not be indicative of results obtained in later preclinical studies and clinical trials.

Conducting preclinical testing is a lengthy, time-consuming and expensive process. The length of time of such testing may vary substantially according to the type, complexity and novelty of the program, and often can be several years or more per program. Delays associated with programs for which we are conducting preclinical testing and studies may cause us to incur additional operating expenses. We may experience unexpected or adverse results in our ongoing or future clinical trials. We will be required to demonstrate through adequately designed and executed clinical trials that our product candidates are safe and effective, with a favorable benefit-risk profile, for use in their target indications before we can seek regulatory approvals for their commercial sale. Our initial clinical trials have started with relatively small cohorts before expanding in size in subsequent cohorts. If safety issues arise in an early cohort, we may be delayed or prevented from subsequently expanding into larger trial cohorts. Earlier gene therapy clinical trials conducted by others also utilized adeno-associated viral, or AAV, vectors. However, these studies should not be relied upon as evidence that our planned clinical trials will succeed. Trial designs and results from previous trials are not necessarily predictive of our future clinical trial designs or results, and initial positive results we may observe may not be confirmed upon full analysis of the complete trial data. In addition, the positive results we have observed for our product candidates in preclinical animal models may not be predictive of our future clinical trials in humans. Our product candidates may also fail to show the desired safety and efficacy in later stages of clinical development even if they successfully advance through initial clinical trials.

Preliminary, topline or interim data from our clinical trials that we or our partners announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we have made, and may continue to make, public preliminary, topline or interim data from our clinical trials, including preliminary biomarker data. Preliminary or topline data from clinical trials remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary or topline data that were previously made public. Interim data from clinical trials that we may complete are also subject to the risk that one or more of the clinical outcomes may materially change as subject enrollment continues and more data become available. As a result, preliminary, topline and interim data should be viewed with caution until the final data are available. Adverse differences between preliminary, topline or interim data and final data could significantly harm our reputation and business prospects.

If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our products may be delayed.

From time to time, we estimate the timing of the accomplishment of various scientific, clinical, regulatory, manufacturing and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of preclinical studies and clinical trials, the release of data from such studies and the submission of regulatory filings, including IND submissions. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are, and will be, based on a variety of assumptions. The actual timing of these milestones can vary significantly compared to our estimates, in some cases for reasons beyond our control. We may experience numerous unforeseen events during, or as a result of, any future clinical trials that we conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates.

Gene therapy is a novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval. Currently, only a limited number of gene therapy products have been approved in the United States and in foreign countries.

Our current product candidates are based on gene therapy technology and our future success depends on the successful development of this novel therapeutic approach. The regulatory requirements that govern any novel gene therapy product candidates we develop are not entirely clear and are subject to change. The clinical study requirements of the FDA and ex-U.S. regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the

potential products. The regulatory approval process for novel product candidates such as ours may be more expensive and take longer than for other, better known or extensively studied product candidates. Further, as we are developing novel treatments for diseases in which there is little clinical experience with new endpoints and methodologies, there is heightened risk that the FDA or comparable foreign regulatory bodies may not consider the clinical trial endpoints to provide clinically meaningful results, and the resulting clinical data and results may be more difficult to analyze. To date, only a limited number of gene therapy products have been approved in the United States and foreign countries, which makes it difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States or other jurisdictions. Further, approvals by ex-U.S. regulatory agency may not be indicative of what the FDA may require for approval, or vice versa.

Our product candidates may cause undesirable and unforeseen side effects, which could delay or prevent their advancement into clinical trials or regulatory approval, limit the commercial potential or result in significant negative consequences.

While new AAV vectors have been developed to reduce side effects previously reported in third-party gene therapy treatments, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material.

For example, in our clinical study for PBKR03, for which, in order to reduce operating expenses, we have stopped further clinical development and are exploring strategic alternatives for this asset, a patient experienced a grade 4 serious adverse event of acute communicating hydrocephalus. Additional possible adverse side effects that could occur with treatment with gene therapy products include an immunologic reaction early after administration which, while not necessarily adverse to the patient's health, could substantially limit the effectiveness of the treatment. For example, in previous third-party clinical trials involving AAV vectors for gene therapy, some subjects experienced the development of a T-cell immune response, whereby after the vector is within the target cells, the cellular immune response system triggers the removal of transduced cells by activated T-cells. Other recent clinical trials involving high doses of AAV vectors have also resulted in liver damage and death. Further, following administration of any AAV vector, patients are likely to develop NAbs specific to the vector administered. Other preclinical studies have suggested that high dosages of AAV administration may result in toxicity due to degeneration of the dorsal root ganglia. Preliminary results of our NHP toxicology studies for our PBGM01 and PBFT02 product candidates have demonstrated trigeminal ganglia and dorsal root ganglia toxicity. Based on these results, and if our vectors demonstrate a similar effect in other programs, we may decide or be required to perform additional preclinical studies or to halt or delay further clinical development of our product candidates.

In addition to side effects caused by the product candidate, the administration process or related procedures also can cause adverse side effects. Each of our clinical product candidates are expected to utilize ICM administration. While this method of administration has been available for decades, its use for therapies is relatively new, no therapies are currently approved using ICM administration, and it may be perceived as having greater risk than more common methods of administration, such as intravenous injection. If any such adverse events occur, our clinical trials could be suspended or terminated. If we cannot demonstrate that any adverse events were not caused by the drug or administration process or related procedures, the FDA or ex-U.S. regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to not initiate, delay, suspend or terminate any future clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects significantly.

Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategies, or REMS, to ensure that the benefits of the product outweigh its risks, which may include, among other things, a Medication Guide outlining the risks of the product for distribution to patients and a

communication plan to health care practitioners. Furthermore, if we or others later identify undesirable side effects caused by our product candidate, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings in the labeling;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these occurrences may harm our business, financial condition and prospects significantly.

Adverse public perception of genetic medicines may negatively impact regulatory approval of, and/or demand for, our potential products.

Regulatory approval of and/or demand for our potential products will depend in part on public acceptance of the use of genetic medicine for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that genetic medicines are unsafe, unethical or immoral, and consequently, our products may not gain the acceptance of the public or the medical community. Adverse public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop.

There have been several significant adverse side effects reported in genetic medicine treatments in the past. For example, in 1999, there was public backlash against gene therapy following the death of a clinical trial subject in a gene therapy clinical trial that utilized an adenovirus vector. It was later discovered that adenoviruses could generate an extreme immune system reaction that can be life threatening. Dr. Wilson, our Chief Scientific Advisor, was a co-investigator of the 1999 trial while he was Director of the Institute for Human Gene Therapy of Penn. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy by us or our competitors, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception and potential regulatory delays in the clinical testing or approval of our product candidates.

As an organization, we have limited experience designing and implementing clinical trials and we have never conducted pivotal clinical trials. Failure to adequately design a trial, or incorrect assumptions about the design of the trial, could adversely affect the ability to initiate the trial, enroll patients, complete the trial, or obtain regulatory approval on the basis of the trial results, as well as lead to increased or unexpected costs.

The design and implementation of clinical trials is a complex process. As an organization, we have limited experience designing and implementing clinical trials, and we may not successfully or cost effectively design and implement clinical trials that achieve our desired clinical endpoints efficiently, or at all. A clinical trial that is not well designed may delay or even prevent initiation of the trial, can lead to increased difficulty in enrolling patients, may make it more difficult to obtain regulatory approval for the product candidate on the basis of the study results, or, even if a product candidate is approved, could make it more difficult to commercialize the product successfully or obtain reimbursement from third-party payors. Additionally, a trial that is not well designed could be inefficient or more expensive than it otherwise would have been, or we may incorrectly estimate the related expenses to implement the clinical trial, which could lead to a shortfall in funding.

The disorders we seek to treat have low incidence and prevalence, and it may be difficult to identify patients with these disorders, which may lead to delays in enrollment for our trials or slower commercial revenue if approved.

Genetically defined disorders generally, and especially those for which our current product candidates are targeted, have low incidence and prevalence. For example, we estimate the incidence of GM1 in the United States is approximately 1 in 100,000 live births and that there are approximately 3,000 to 6,000 people in the United States with FTD-GRN. There is currently no mandatory screening for GM1. Without mandatory screening, it may be difficult for us to identify a

sufficient number of eligible patients to conduct our clinical trials. These could be significant obstacles to the timely recruitment and enrollment of a sufficient number of eligible patients into our trials. Further, we expect to rely in part on our relationships with the Orphan Disease Center and other patient advocacy groups to assist in identifying eligible patients, and any deterioration of those relationships could impede our ability to successfully enroll patients. Patient enrollment may be affected by other factors including:

- the severity of the disease under investigation;
- design of the study protocol;
- the eligibility criteria for the trial;
- the perceived risks, benefits and convenience of administration of the product candidate being studied;
- our efforts to facilitate timely enrollment in clinical trials;
- the availability of other clinical trials being conducted for the same indication;
- the patient referral practices of physicians; and
- the proximity and availability of clinical trial sites to prospective patients.

Our inability to enroll a sufficient number of patients with these diseases for our planned clinical trials would result in significant delays and could require us to not initiate or abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

Additionally, our projections of both the number of people who have GM1, FTD, and our other product candidates, as well as the people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates, including third-party analyses commissioned by us. The total addressable market opportunity for our product candidates will ultimately depend upon, among other things, the final approved product labeling for each of our product candidates, if our product candidates are approved for sale in our target indications, acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients globally may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our products, or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business. Our products may potentially be dosed on a one-time basis, which means that patients who enroll in our clinical trials may not be eligible to receive our products on a commercial basis if they are approved, leading to lower revenue potential.

Even if we complete the necessary clinical trials, we cannot predict when, or if, we will receive regulatory approval to commercialize a product candidate and the approval may be for a more narrow indication than we seek.

Prior to commercialization, our product candidates must be approved by the FDA pursuant to a BLA in the United States and by similar ex-U.S. regulatory authorities. The process of obtaining marketing approvals, both in the United States and abroad, 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. 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. Our company does not have experience in submitting and supporting the applications necessary to gain marketing approvals. Securing marketing approval requires the submission of extensive preclinical 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 preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate.

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

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials, including the methods for collecting and analyzing data, the statistical analysis plan, and the lack of a concurrent control arm or a decision to use external or historical controls;
- the FDA or comparable foreign regulatory authorities may not agree that the efficacy endpoints used in our clinical trials are appropriate to establish clinical benefit in the intended populations;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that our product candidates are safe and effective for any of their proposed indications;
- development of products for ultra rare diseases, and in particular pediatric diseases, may involve the use of natural history data as an external control. We may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that the control arm(s) are adequate to establish the safety and/or effectiveness of our product candidates;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities a durable response to our product candidates;
- we may be unable to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical programs or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a BLA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the facilities of the third-party manufacturers with which we contract may not be adequate to support approval of our product candidates;
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval; and
- even if our product candidates meet their safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials and the review process.

Regulatory authorities also may approve a product candidate for more limited indications than requested or they may impose significant limitations in the form of narrow indications, warnings or REMS. These regulatory authorities may require precautions or contra indications with respect to conditions of use or they may grant approval subject to the performance of costly post-marketing clinical trials. In addition, regulatory authorities may not approve the product labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates and materially and adversely affect our business, financial condition, results of operations and prospects.

Further, the regulatory authorities may require concurrent approval of a companion diagnostic device. For our product candidates, it may be necessary to use FDA-cleared or FDA-approved diagnostic tests to diagnose patients or to assure the safe and effective use of product candidates in trial subjects. The FDA refers to such tests as in vitro companion diagnostic devices. The FDA has issued guidance describing the agency's current thinking about the development and regulation of in vitro companion diagnostic devices. The final guidance articulates a policy position that, when an in vitro diagnostic device is essential to the safe and effective use of a therapeutic product, the FDA generally will require approval or clearance of the diagnostic device at the same time that the FDA approves the therapeutic product. At this point, it is unclear how the FDA will apply this policy to our current or future gene therapy product candidates. Should the FDA deem genetic tests used for diagnosing patients for our therapies to be in vitro companion diagnostics requiring

FDA clearance or approval, we may face significant delays or obstacles in obtaining approval of a BLA for our product candidates.

The FDA and ex-U.S. regulatory agencies have demonstrated caution in their regulation of gene therapy treatments. Ethical and legal concerns about gene therapy and genetic testing may result in additional regulations or restrictions on the development and commercialization of our product candidates, which may be difficult to predict.

The FDA and ex-U.S. regulatory agencies at both the federal and state level in the United States, U.S. congressional committees, and foreign governments, have expressed interest in further regulating the biotechnology industry, including gene therapy and genetic testing. Any such further regulation may delay or prevent commercialization of some or all of our product candidates.

Regulatory requirements in the United States and abroad governing gene therapy products have changed frequently and may continue to change in the future. In addition to the FDA, the Institutional Biosafety Committee and IRB of each institution at which we conduct our planned clinical trials, would need to review the proposed clinical trial to assess the safety of the trial. Within the FDA, the Office of Tissues and Advanced Therapies, within the Center for Biologics Evaluation and Research, or CBER, consolidates the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee advises CBER on its review. Adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates.

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies or trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of such product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delays as a result of an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all.

Changes in funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, or otherwise prevent new products and services from being developed or commercialized in a timely manner, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop important activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad and will limit our ability to realize their full market potential.

In order to eventually market any of our product candidates in any particular foreign jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a jurisdiction by jurisdiction basis regarding safety and efficacy. Approval by the FDA in the United States, if obtained, does not ensure approval by regulatory authorities in

other countries or jurisdictions. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time-consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. The foreign regulatory approval process involves all of the risks associated with FDA approval. In addition, gene therapy products are considered genetically modified organism, or GMO, products and are regulated as such in each country. Designation of the type of GMO product and subsequent handling and disposal requirements can vary across countries and is variable throughout the European Union. Addressing each specific country requirement and obtaining approval to commence a clinical trial in these countries could result in delays in starting, conducting, or completing a clinical trial. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets and expect to rely on third-party consultants. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our products will be unrealized.

We may not be successful in our efforts to build a pipeline of additional product candidates.

Our business model is centered on developing therapies for patients with CNS disorders by establishing focused selection criteria to select, develop and advance product candidates that we believe will have a high probability of technical and regulatory success through development into commercialization. We may not be able to continue to identify and develop new product candidates in addition to the pipeline of product candidates that we have established through our collaboration with Penn's GTP. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development. For example, they may be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our approach, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

Risks Related to Our Reliance on Third Parties

We currently rely exclusively on our collaboration with GTP and Penn for our preclinical research and development programs, including for discovering, preclinically developing and conducting all IND-enabling studies for our clinical product candidates and our near-term future pipeline. Failure or delay of Penn to fulfil all or part of its obligations to us under the agreement, a breakdown in collaboration between the parties or a complete or partial loss of this relationship would materially harm our business.

Our collaboration with Penn is critical to our current preclinical pipeline. We entered into an amended and restated Research, Collaboration & License Agreement in May 2020, as subsequently amended, or the Penn Agreement, with Penn's GTP to discover and develop certain AAV vector based therapeutics, and the products developed under such collaboration currently represent all of our product pipeline and research programs. We currently rely exclusively on Penn's GTP for all of our preclinical research and development capabilities, and in particular GTP under the direction of Dr. Wilson. Pursuant to the Penn Agreement, Penn's GTP is responsible for discovery, preclinical development activities, including all IND-enabling non-clinical studies and research grade manufacturing, and other collaborative activities set forth in the plan for the funded research. Either party has the right in certain circumstances to terminate the collaboration pursuant to the terms of the Penn Agreement. If Penn's GTP delays or fails to perform its obligations under the Penn Agreement, disagrees with our interpretation of the terms of the collaboration or our discovery plan or terminates our existing agreement, our pipeline of product candidates would be significantly adversely affected and our prospects will be materially harmed.

The term of the research funding portion of the Penn Agreement, under which we have the ability to acquire exclusive rights to additional gene therapy products for CNS indications, expires in August 2026. In addition, the discovery program, under which we have rights to new technologies for our product candidates is currently also set to expire in

August 2026. The term of the exploratory research program in large indications, initially TLE, expires in August 2024. If we seek to extend or alter the terms of our collaboration, we will need to negotiate a new or amended agreement, which may not be available to us on equally favorable terms, if at all. Penn has also entered into collaborations with third parties, including certain of our competitors, addressing targets and disease indications outside the scope of our collaboration. As a result, Penn may have competing interests with respect to their priorities and resources. We may have disagreements with Penn with respect to the interpretation of the Penn Agreement, use of resources or otherwise that could cause our relationship with Penn to deteriorate. As a result, Penn may reduce their focus on, and resources allocated to, our programs, potentially delaying or terminating our ability to advance product candidates through preclinical studies. Additionally, if Dr. Wilson were to leave Penn or to otherwise no longer be meaningfully involved with us, our preclinical research and development capabilities may be substantially reduced.

Further, under the Penn Agreement, Penn is primarily responsible for prosecuting and maintaining our licensed intellectual property, and it may fail to properly prosecute, maintain or defend such intellectual property. In such event, if we are unable to otherwise maintain or defend such intellectual property, we could face the potential invalidation of the intellectual property or be subjected to litigation or arbitration, any of which would be time-consuming and expensive. To enforce the licensed intellectual property rights under the Penn Agreement, we will need to coordinate with Penn, which could slow down or hamper our ability to enforce our licensed intellectual property rights. In such event, we could face increased competition that could materially and adversely affect our business.

We rely on third parties to conduct our preclinical studies and clinical trials and rely on them to perform other tasks for us. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

Although we have recruited a team that has experience with clinical trials, as a company we have limited experience in conducting clinical trials. Moreover, we currently rely exclusively on Penn for our discovery and preclinical research and will continue to rely upon medical institutions, clinical investigators, contract laboratories and other third parties, or our CROs, to conduct clinical trials for our product candidates. We expect to rely heavily on these parties for execution of preclinical and clinical trials for our product candidates and control only certain aspects of their activities. If these parties reduce the levels of efforts and resources to our product candidate activities, prioritize work with a competitor of ours or if a dispute were to arise between us and these parties, they may not meet our expected deadlines or provide us with sufficient materials for our regulatory filings. Nevertheless, we will be responsible for ensuring that each of our preclinical and clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards and our reliance on CROs will not relieve us of our regulatory responsibilities. For any violations of laws and regulations during the conduct of our preclinical studies and clinical trials, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

We, Penn and our CROs will be required to comply with regulations, including cGCPs for conducting, monitoring, recording and reporting the results of preclinical and clinical trials to ensure that the data and results are scientifically credible and accurate and that the trial patients are adequately informed of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any drugs in clinical development. The FDA enforces cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators, and trial sites. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our future clinical trials will comply with cGCPs. In addition, our clinical trials must be conducted with product candidates produced in accordance with the requirements in cGMP regulations. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action.

Although we currently design and intend to continue designing our planned clinical trials for our product candidates, for the foreseeable future CROs will conduct all of our planned clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third

parties to conduct future preclinical studies and clinical trials will also result in less day-to-day control over the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any preclinical studies or clinical trials with which such CROs are associated with may be extended, delayed or terminated. In such cases, we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates in the subject indication could be harmed, our costs could increase and our ability to generate revenue could be delayed.

We rely on third parties to conduct our clinical trials. If those third parties do not perform as contractually required, fail to satisfy legal or regulatory requirements, miss expected deadlines or terminate the relationship, our development program could be delayed with potentially material and adverse effects on our business, financial condition, results of operations and prospects.

We rely on third-party clinical investigators, CROs, clinical data management organizations and consultants to assist or provide the design, conduct, supervision and monitoring of clinical trials of our product candidates. Because we rely and intend to rely on these third parties and will not have the ability to conduct all clinical trials independently, we will have less control over the timing, quality and other aspects of clinical trials than we would have had we conducted them on our own. These investigators, CROs and consultants will not be our employees and we will have limited control over the amount of time and resources that they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw time and resources from our programs. The third parties with which we may contract might not be diligent, careful or timely in conducting our clinical trials, resulting in the clinical trials being delayed or unsuccessful.

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. In all events, we will be responsible for ensuring that each of our preclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial as well as applicable legal and regulatory requirements. The FDA generally requires preclinical studies to be conducted in accordance with GLPs and clinical trials to be conducted in accordance with cGCPs, including for designing, conducting, recording and reporting the results of preclinical studies and clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. Our reliance on third parties that we do not control will not relieve us of these responsibilities and requirements. Any adverse development or delay in our preclinical studies or clinical trials as a result of our reliance on third parties could have a material and adverse effect on our business, financial condition, results of operations and prospects.

If any of our relationships with these third-party CROs or others terminate, we may not be able to enter into alternative arrangements or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which can materially adversely impact our ability to meet our desired clinical development timelines.

We may in the future enter into collaborations with other third parties for the discovery, development and commercialization of our product candidates. If any of our current or future collaborators cease development efforts under our collaboration agreements, or if any of those agreements are terminated, these collaborations may fail to lead to commercial products and we may never receive milestone payments or future royalties under these agreements.

We may in the future enter into third-party collaborations for research, development and commercialization of other therapeutic technologies or product candidates. Biotechnology companies are our likely future collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements.

With any future collaboration agreements, we expect to have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Moreover, our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Our potential future collaborations involving our product candidates may pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on preclinical studies or clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to litigation or potential liability;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation, indemnification obligations and potential liability;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management attention and resources; collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates;
- if a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated; and
- collaboration agreements may restrict our right to independently pursue new product candidates.

As a result of the foregoing, any future collaboration agreements may not lead to development or commercialization of our product candidates in the most efficient manner or at all. If a collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated. Any failure to successfully develop or commercialize our product candidates pursuant to our current or any future collaboration agreements could have a material and adverse effect on our business, financial condition, results of operations and prospects.

Moreover, to the extent that any of our existing or future collaborators were to terminate a collaboration agreement, we may be forced to independently develop our product candidates and research programs, including funding preclinical studies or clinical trials, assuming marketing and distribution costs and maintaining and defending intellectual property rights, or, in certain instances, abandon product candidates altogether, any of which could result in a change to our business plan and have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We may decide to pursue collaborations with additional pharmaceutical and biotechnology companies for the development and potential commercialization of some of our product candidates. In particular, we recently announced that we are looking for strategic partners for our MLD and Krabbe clinical programs. We face significant competition in seeking appropriate collaborators. Any new collaboration may be on terms that are not optimal for us, and we may not be able to maintain any new collaboration if, for example, development or approval of a product candidate is delayed, sales of an approved product candidate do not meet expectations or the collaborator terminates the collaboration. In addition, a significant number of recent business combinations among large pharmaceutical companies has resulted in a reduced number of potential future collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of any additional collaborations or other arrangements that we may establish may not be favorable to us.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or 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 increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

We may have conflicts with our collaborators that could delay or prevent the development or commercialization of our product candidates.

We may have conflicts with our collaborators, including Penn, such as conflicts concerning the interpretation of preclinical or clinical data, the achievement of milestones, the interpretation of contractual obligations, payments for services, development obligations or the ownership of intellectual property developed during our collaboration. If any conflicts arise with any of our collaborators, including Penn, such collaborator may act in a manner that is adverse to our best interests. Any such disagreement could result in one or more of the following, each of which could delay or prevent the development or commercialization of our product candidates, and in turn prevent us from generating revenues: unwillingness on the part of a collaborator to pay us milestone payments or royalties we believe are due to us under a collaboration, which could require us to raise additional capital; uncertainty regarding ownership of intellectual property rights arising from our collaborative activities, which could prevent us from entering into additional collaborations;

unwillingness by the collaborator to cooperate in the development or manufacture of the product, including providing us with product data or materials; unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities or to permit public disclosure of the results of those activities; initiating of litigation or alternative dispute resolution options by either party to resolve the dispute; or attempts by either party to terminate the relevant agreement.

We may in the future seek to engage in strategic transactions to acquire or in-license new products, product candidates or technologies. If we are unable to successfully complete, or realize the benefits from, such transactions it may adversely affect our ability to develop and commercialize product candidates, impact our cash position, increase our expenses and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as additional collaborations, acquisitions of companies, asset purchases, joint ventures and in-licensing of new products, product candidates or technologies that we believe will complement or augment our existing business. If we acquire assets with promising markets or technologies, we may not be able to realize the benefit of acquiring such assets if we are not able to successfully integrate them with our existing technologies. We may encounter numerous difficulties in developing, testing, manufacturing and marketing any new products resulting from a strategic acquisition that delay or prevent us from realizing their expected benefits or enhancing our business.

We cannot assure you that following any such strategic transaction, we will achieve the expected synergies to justify the transaction. For example, such transactions may require us to incur non-recurring or other charges, increase our near- and long-term expenditures and pose significant integration or implementation challenges or disrupt our management or business. These transactions would entail numerous operational and financial risks, including exposure to unknown liabilities, disruption of our business and diversion of our management's time and attention in order to manage a collaboration or develop acquired products, product candidates or technologies, incurrence of substantial debt or dilutive issuances of equity securities to pay transaction consideration or costs, higher than expected acquisition or integration costs, write-downs of assets or goodwill or impairment charges, increased amortization expenses, difficulty and cost in facilitating the transaction or combining the operations and personnel of any acquired business, impairment of relationships with key suppliers, manufacturers or customers of any acquired business due to changes in management and ownership and the inability to retain key employees of any acquired business.

Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and would have a material and adverse effect on our business, financial condition, results of operations and prospects. Conversely, any failure to enter any strategic transaction that would be beneficial to us could delay the development and potential commercialization of our product candidates and have a negative impact on the competitiveness of any product candidate that reaches market.

Risks Related to Manufacturing

Gene therapies are novel, complex and difficult to manufacture. We could experience manufacturing problems that result in delays in our development or commercialization programs or otherwise harm our business.

We currently rely on third parties to develop, manufacture and test clinical supplies of our product candidates, including the materials used to administer our product candidates. For our initial clinical trials, we rely on the manufacturing facility of Catalent Maryland (formerly Paragon Bioscience), or Catalent, for supply of our product candidates. We have limited experience as a company in developing manufacturing facilities. If or when we decide to construct our own manufacturing facility for long-term commercial market supply, we may face delays in building out a plant, constructing new facilities, transferring technology to the facilities or hiring experts to staff and operate the facilities and, accordingly, our production capacity could be limited. We have established internal testing operations supporting our preclinical and clinical manufacturing in addition to using external contract testing labs and established analytical development and process development capabilities to support our pipeline. The manufacturing processes used to produce our product candidates are complex, novel and have not been validated for commercial use. Many factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or

contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers.

Our product candidates require processing steps that are more complex than those required for most small molecule drugs. Moreover, unlike small molecules, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product is consistent from lot-to-lot or will perform in the intended manner. Accordingly, we employ multiple steps to control the manufacturing process to assure that the process works consistently and the product candidate is made strictly and consistently in compliance with the process. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, low lot yields, product recalls, product liability claims or insufficient inventory. As a result, we may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet the FDA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, the FDA and ex-U.S. regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA or ex-U.S. regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures, low lot yields or product recalls. Lot failures, low lot yields or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We, or our third-party collaborators, also may encounter problems hiring and retaining the experienced scientific, quality-control and manufacturing personnel needed to operate our manufacturing processes, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements.

Any problems in our, or our third-party collaborators', manufacturing process or facilities could result in delays in our planned clinical trials and increased costs, and could make us a less attractive collaborator for potential partners, including larger biotechnology companies and academic research institutions, which could limit our access to additional attractive development programs. It could also require us to find alternative manufacturing processes, which may be unavailable to us on attractive terms, or at all. Problems in our manufacturing process could restrict our ability to meet potential future market demand for our products.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates proceed through preclinical studies to late-stage clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the materials manufactured using altered processes. Such changes may also require additional testing, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue.

We currently rely and expect to continue to rely on third-party manufacturers to produce clinical supply of our product candidates, and we have not entered into binding agreements with any such manufacturers to support commercialization. The competition for gene therapy contract development, manufacturing and testing services is intense. Additionally, these manufacturers do not have experience producing our product candidates at commercial levels and may not achieve the necessary regulatory approvals or produce our product candidates at the quality, quantities, locations and timing needed to support commercialization.

While we are in the process of establishing manufacturing capability for certain clinical manufacturing activities, we do not currently plan to independently manufacture most of the material for our planned clinical programs. We currently

rely, and expect to continue to rely, on third parties for the production of our preclinical study and planned clinical trial materials, including the materials used to administer our product candidates and, therefore, we can control only certain aspects of their activities. The competition for gene therapy contract development, manufacturing and testing is intense. Reliance on third-party manufacturers may expose us to different risks than if we were to manufacture product candidates ourselves, including but not limited to potential competition from other genetic biotechnology companies for the use of such third-party manufacturers.

While we have secured an agreement with Catalent to manufacture clinical supply of our product candidates, we have not yet secured manufacturing capabilities for commercial quantities of our product candidates. To date, while we have a collaboration agreement with Catalent for a dedicated clean room suite, we have only entered into agreements with such manufacturer to support our clinical studies. We may be unable to negotiate binding agreements with the manufacturers to support our potential commercialization activities at commercially reasonable terms.

Before any of our third-party manufacturers and suppliers can begin to commercially manufacture our product candidates, including the materials used to administer our product candidates, they must demonstrate to regulatory authorities that the planned chemistry, manufacturing and controls for our gene therapy product candidates meet certain requirements. Manufacturing of product candidates for clinical and commercial purposes must comply with the cGMP and applicable ex-U.S. regulatory requirements. The cGMP requirements govern quality control and documentation policies and procedures. Complying with cGMP and ex-U.S. regulatory requirements will require that we expend time, money and effort in production, recordkeeping and quality control to assure that our product candidates meet applicable specifications and other requirements. Our third-party manufacturers' also must demonstrate to the FDA and ex-U.S. regulators that they can make the product candidate in accordance with the cGMP requirements as part of a pre-approval inspection prior to FDA or similar ex-U.S. regulatory approval of the product candidate. Failure to pass a pre-approval inspection might significantly delay our ability to begin trials in the respective jurisdiction and FDA and ex-U.S. regulatory approval of our product candidates. If any of our third-party manufacturers fail to comply with these requirements, we would be subject to possible regulatory action, which could limit the jurisdictions in which we are permitted to sell our products. As a result, our business, financial condition and results of operations may be materially harmed.

In addition, our third-party manufacturers may fail to comply with cGMP regulations or similar regulatory requirements outside the United States. 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 or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates.

Even if our third-party manufacturers comply with applicable regulatory requirements, we cannot assure you that they will be able to successfully manufacture additional product candidates at a larger scale in a timely or economical manner, or at all. If they are unable to successfully increase our manufacturing scale or capacity, the development, testing, and clinical trials of our product candidates may be delayed or infeasible, and regulatory approval or commercial launch of any resulting product may be delayed or not obtained, which could significantly harm our business.

Our third-party manufacturers and suppliers use biological materials and may use hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time-consuming or costly.

Our third-party manufacturers and suppliers may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety or the environment. The operations of our third-party manufacturers and suppliers also produce hazardous waste products. Federal, state, and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of

contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

Any contamination in our third parties' manufacturing process, shortages of raw materials, labor or reagents or failure of any of our key suppliers to deliver necessary components of our platform could result in delays in our clinical development or marketing schedules.

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could materially adversely affect our or our third-party vendor's ability to produce our gene therapies on schedule and could therefore harm our results of operations and cause reputational damage.

The raw materials required in our third-party vendors manufacturing processes are derived from biological sources. We cannot assure that our third-party vendors have, or will be able to obtain on commercially reasonable terms, or at all, sufficient rights to these materials derived from biological sources. Such raw materials are difficult to procure and may also be subject to contamination or recall. A material shortage, contamination, recall, or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the clinical and commercial manufacturing of our product candidates, which could materially and adversely affect our operating results and development timelines.

We rely on third-party suppliers for the supply and manufacture of certain components of our technology. Should our ability to procure these material components from our suppliers be compromised, our ability to continuously operate would be impaired until an alternative supplier is sourced, qualified and tested, which could limit our ability to produce a clinical and commercial supply of our product candidates and harm our business.

We depend on third-party suppliers for materials used in the manufacture of our product candidates, and the loss of these third-party suppliers or their inability to supply us with adequate materials could harm our business.

We rely on third-party suppliers for certain materials and components required for the production of our product candidates, including the materials used to administer our product candidates. Our dependence on these third-party suppliers and the challenges we may face in obtaining adequate supplies of materials involve several risks, including limited control over pricing, availability, and quality and delivery schedules. There is substantial demand and limited supply for certain of the raw materials used to manufacture gene therapy products. As a small company, our negotiation leverage is limited and we are likely to get lower priority than our competitors that are larger than we are. We cannot be certain that our suppliers will continue to provide us with the quantities of these raw materials that we require or satisfy our anticipated specifications and quality requirements. Any supply interruption in limited or sole sourced raw materials could materially harm our ability to manufacture our product candidates until a new source of supply, if any, could be identified and qualified. We may be unable to find a sufficient alternative supply channel in a reasonable time or on commercially reasonable terms. Any performance failure on the part of our suppliers could delay the development and potential commercialization of our product candidates, including limiting supplies necessary for clinical trials and regulatory approvals, which would have a material adverse effect on our business.

Risks Related to Commercialization

We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies or technologies that are more advanced or effective than ours, which may harm our business and financial condition, and our ability to successfully market or commercialize our product candidates.

The biotechnology and pharmaceutical industries, including the genetic medicines field, are characterized by rapidly changing technologies, competition and a strong emphasis on intellectual property. We are aware of several companies focused on developing gene therapies in various indications as well as several companies addressing methods for modifying genes and regulating gene expression. We may also face competition from large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

For the treatment of GM1, there are no approved disease-modifying therapies. We consider our most direct competitor with respect to PBGM01 for the treatment of GM1 to be Lysogene, S.A, or Lysogene. Lysogene is conducting a Phase 1/2 clinical trial for a gene therapy treatment administered via ICM for early and late infantile GM1.

For the treatment of FTD, there are no approved disease-modifying therapies. We consider our most direct competitors with respect to PBFT02 for the treatment of FTD-GRN to be Alector, Inc. (partnered with GlaxoSmithKline), which is enrolling a Phase 3 clinical trial with a humanized anti-human sortilin monoclonal antibody for FTD-GRN, and Prevail Therapeutics Inc. (now part of Eli Lilly & Co), which has initiated a Phase 1/2 clinical trial for a gene therapy treatment for FTD-GRN, and is expected to continue enrolling into 2023. Several other companies, including Applied Genetic Technologies Corporation (recently acquired by Syncona), Orchard Therapeutics plc, Sinfonia Biotherpeutics, QurAlis and Aviado Therapeutics, are conducting preclinical research using gene therapy approaches to treat FTD-GRN patients. AviadoBio Ltd has reported the planned initiation of a phase 1/2 trial in 2023. Denali Therapeutics Inc. in partnership with Takeda Pharmaceutical Company Limited began recruitment of a Phase 1/2 clinical trial for their recombinant progranulin protein in addition to their oral EIF2a modulator already in a Phase 1 clinical trial. We are also aware of other therapeutic approaches in preclinical development that may target FTD-GRN patients.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical, and other resources than we do, such as larger research and development, clinical, commercial and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any product candidates that we may develop. Competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market, if ever. Additionally, new or advanced technologies developed by our competitors may render our current or future product candidates uneconomical or obsolete, and we may not be successful in commercializing our product candidates against competitors.

The commercial success of any of our product candidates will depend upon its degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Ethical, social and legal concerns about gene therapy could result in additional regulations restricting or prohibiting our products. Even with the requisite approvals from the FDA in the United States and other ex-U.S. regulatory authorities, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients (which includes caregivers when applicable) and health care payors of gene therapy products in general, and our product candidates in particular, as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including:

- the efficacy, durability and safety of such product candidates as demonstrated in clinical trials;
- the potential and perceived advantages of product candidates over alternative treatments;
- the cost of treatment relative to alternative treatments;
- the clinical indications for which the product candidate is approved by the FDA or ex-U.S. regulatory authorities;
- the willingness of physicians to order genetic testing for potential target patient populations;
- the willingness of potential patients to have genetic testing and counseling;
- the willingness of physicians to prescribe new therapies, including therapies using ICM administration;
- our ability to successfully train neurosurgeons and interventional radiologists in ICM administration of our product candidates;
- the willingness of the target patient population to try new therapies and a therapy with ICM administration;
- the prevalence and severity of any side effects;

- product labeling or product insert requirements of the FDA or ex-U.S. regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products and the perceptions of such competitive products compared to our products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party payor coverage and adequate reimbursement and patients' willingness to pay out-of-pocket in the absence of such coverage and adequate reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be fully known until after it is launched.

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 and we may not be able to generate any revenue.

We currently do not have a sales team or marketing team for the sales, marketing, and distribution of any of 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 sales, reimbursement, 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 team with technical expertise and supporting distribution capabilities to commercialize our product candidates, which will be expensive and time-consuming and will require significant attention of our executive officers to manage. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of any of our product candidates that we obtain approval to market.

With respect to the commercialization of all or certain of our product candidates, we may choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. If we are unable to enter into such arrangements when needed on acceptable terms, or at all, we may not be able to successfully commercialize any of our product candidates that receive regulatory approval or any such commercialization may experience delays or limitations. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future product revenue will suffer and we may incur significant additional losses.

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

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay the pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to timely capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. The development of our clinical product candidates and ongoing research programs require significant resources. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Risks Related to Intellectual Property

If we are unable to obtain and maintain patent protection or other necessary rights for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad or our rights under licensed patents is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected.

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other countries for our current product candidates and future products, as well as our core technologies, including our manufacturing know-how. We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business by seeking, maintaining and defending our intellectual property, whether developed internally or licensed from third parties. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene therapy. Additionally, for some of our product candidates, we intend to rely on regulatory protection afforded through rare drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available.

Currently, most of our intellectual property protection consists of patent applications that we have in-licensed from Penn under the Penn Agreement. The in-licensed patent applications are directed to certain new AAV capsids, to recombinant AAV viruses, or rAAV, capable of delivering certain genes into human cells to treat monogenic disorders of the CNS, to methods of treating those monogenic diseases with rAAV, as well as to certain aspects of our manufacturing capabilities and related technologies.

We also have options under the Penn Agreement to add additional intellectual property to our existing license.

Our intellectual property further includes a patent application that we solely own that covers processes for manufacturing rAAV.

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 degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our licensed patent applications will mature into issued patents, and cannot provide any assurances that any such patents, if issued, will include claims with a scope sufficient to protect our current and future product candidates or otherwise provide any competitive advantage. Additionally, patents can be enforced only in those jurisdictions in which the patent has issued. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally twenty years after its first nonprovisional U.S. filing. The natural expiration of a patent outside of the United States varies in accordance with provisions of applicable local law, but is generally 20 years from the earliest local filing date. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. 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.

Moreover, our exclusive license is subject to field restrictions and retained rights, which may adversely impact our competitive position. Our licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates, including biosimilar versions of such products. In addition, the patent portfolio licensed to us is, or may be, licensed to third parties outside our licensed field, and such third parties may have certain enforcement rights. Thus, patents licensed to us could be put at risk of being invalidated or interpreted narrowly in litigation filed by or against another licensee or in administrative proceedings brought by or against another licensee in response to such litigation or for other reasons.

Other parties have developed technologies that may be related or competitive to our own and such parties may have filed or may file patent applications, or may have received or may receive patents, claiming inventions that may overlap or conflict with those claimed in our own patent applications or issued patents. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and in 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 the inventors of our licensed patents and applications were the first to make the inventions claimed in those patents or pending patent applications, or that they were the first to file for patent protection of such inventions. Further, we cannot assure you that all of the potentially relevant prior art relating to our licensed patents and patent applications has been found. If such prior art exists, it can invalidate a patent or prevent a patent from issuing from a pending patent application. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty. Further, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

In addition, the patent prosecution process is expensive and time-consuming, and we or our licensors may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, the scope of the claims initially submitted for examination may be significantly narrowed by the time they issue, if at all. It is also possible that we or our licensors will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We cannot provide any assurances that we will be able to pursue or obtain additional patent protection based on our research and development efforts, or that any such patents or other intellectual property we generate will provide any competitive advantage. Moreover, we do not have the right to control the preparation, filing and prosecution of patent applications, or to control the maintenance of the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be filed, prosecuted or maintained in a manner consistent with the best interests of our business.

Even if we acquire patent protection that we expect should enable us to maintain competitive advantage, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability. Third parties, including competitors, may challenge the inventorship, scope, validity, or enforceability thereof, which may result in such patents being narrowed, invalidated or held unenforceable. If issued, our licensed patents may be challenged in patent offices in the United States and international markets, or in court. For example, we may be subject to a third-party submission of prior art to the U.S. Patent and Trademark Office, or USPTO, challenging the validity of one or more claims of our licensed patents, once issued. Such submissions may also be made prior to a patent's issuance, precluding the granting of a patent based on one of our pending licensed patent applications. We may become involved in opposition, reexamination, *inter partes* review, post-grant review, derivation, interference, or similar proceedings in the United States or abroad challenging the claims of patents that we have licensed, once issued. Furthermore, patents that we have licensed may be challenged in court, once issued. Competitors may claim that they invented the inventions claimed in such patents or patent applications prior to the inventors of our licensed patents, or may have filed patent applications before the inventors of our licensed patents did. A competitor may also claim that we are infringing its patents and that we therefore cannot practice our technology as claimed under our licensed patent applications and patents, if issued. As a result, one or more claims of our licensed patents may be narrowed or invalidated. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose our rights to those challenged patents.

Even if they are unchallenged, our licensed patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our licensed patents by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, even if we have a valid and enforceable patent, we may not be able to exclude others from practicing our invention if the other party can show that they used the invention in commerce before our filing date or the other party benefits from a compulsory license. Moreover, a third party may develop a competitive product that provides benefits similar to one or more of our product candidates but that uses a vector or an expression construct that falls outside the scope of our patent protection or license rights. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected, which would harm our business.

Similar risks would apply to any patents or patent applications that we may own or in-license in the future.

In addition to patent protection, if any of our product candidates are approved by the FDA as a biological product under a BLA in the United States, we believe the product would qualify for a 12-year period of exclusivity. Other regulatory

exclusivities may be available, such as Orphan Drug exclusivity, with analogous data, marketing, and orphan exclusivities in various foreign countries. However, the scope of such regulatory exclusivities is subject to change, and may not provide us with adequate and continuing protection sufficient to exclude others from commercializing products similar to our product candidates.

All of our current product candidates and research programs are licensed from or based upon licenses from a third - party and are field limited to certain indications. If this license agreement is terminated or interpreted to narrow our rights, our ability to advance our current product candidates or develop new product candidates based on these technologies will be materially adversely affected.

We now depend on Penn, and will continue to depend on Penn and on licenses and sublicenses from other third parties, as well as potentially on other strategic relationships with third parties, for the research, development, manufacturing and commercialization of our current product candidates. If any of our licenses or relationships or any in-licenses on which our licenses are based are terminated or breached, we may:

- lose our rights to develop and market our current product candidates;
- lose patent or trade secret protection for our current product candidates;
- experience significant delays in the development or commercialization of our current product candidates;
- not be able to obtain any other licenses on acceptable terms, if at all; or
- incur liability for damages.

Additionally, even if not terminated or breached, our intellectual property licenses or sublicenses may be subject to disagreements over contract interpretation which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations.

If we experience any of the foregoing, it could have a materially adverse effect on our business and could force us to cease operations which could cause you to lose all of your investment.

If we breach our license agreements it could have a material adverse effect on our commercialization efforts for our product candidates.

If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties, we could lose license rights that are important to our business. Our current clinical product candidates and pipeline are and our anticipated near term pipeline will be, licensed from Penn.

Under the Penn Agreement, we are subject to various obligations, including payment obligations, diligence obligations such as development and commercialization obligations, as well as potential royalty payments and other obligations. If we fail to comply with any of these obligations or otherwise breach our license agreements, our licensors may have the right to terminate the applicable license in whole or in part. Generally, the loss of any one of our current licenses, or any other license we may acquire in the future, could harm our business, prospects, financial condition and results of operations.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other intellectual property rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations;

- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- whether and the extent to which inventors are able to contest the assignment of their rights to our licensors.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms or at all, we may be unable to successfully develop and commercialize the affected product candidates. In addition, if disputes arise as to ownership of licensed intellectual property, our ability to pursue or enforce the licensed patent rights may be jeopardized. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

Our strategy of obtaining rights to key technologies through in-licenses may not be successful.

We seek to expand our product candidate pipeline in part by in-licensing the rights to key technologies. The future growth of our business will depend in part on our ability to in-license or otherwise acquire the rights to additional product candidates or technologies. We cannot assure you that we will be able to in-license or acquire the rights to any product candidates or technologies from third parties on acceptable terms or at all.

The in-licensing and acquisition of these technologies is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire product candidates or technologies 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 license rights to us. Furthermore, we may be unable to identify suitable product candidates or technologies within our area of focus. If we are unable to successfully obtain rights to suitable product candidates or technologies, our business, financial condition and prospects could suffer.

Third parties may initiate legal proceedings alleging claims of intellectual property infringement, 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 future products and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and frequent litigation regarding patents and other intellectual property rights. We may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates, future products and technology. Our competitors or other third parties may assert infringement or misappropriation claims against us, alleging that our therapeutics, manufacturing methods, formulations or administration methods are covered by their patents. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing product candidates. For example, a third party previously sent us a letter claiming that the use of our AAVhu68 capsid infringes certain patent claims to which the third party has an exclusive license . While this matter has been resolved and we believe that we would have valid defenses to these and any other such claims; however, if any such claims were ultimately successful, we might require a license to continue to use and sell any product candidates using such AAV vector. Such licenses may not be available on commercially reasonable terms, or at all.

Further, we do not know which processes we will use for commercial manufacture of our future products, or which technologies owned or controlled by third parties may prove important or essential to those processes. Given the vast number of patents in our field of technology, we cannot be certain or guarantee that we do not or will not infringe existing patents or that we will not infringe patents that may be granted in the future. Many companies have filed, and continue to file, patent applications related to gene therapy and orphan diseases. Some of these patent applications have already been allowed or issued and others may issue in the future. Since this area is competitive and of strong interest to pharmaceutical and biotechnology companies, there will likely be additional patent applications filed and additional patents granted in the future, as well as additional research and development programs expected in the future. Furthermore, because patent applications can take many years to issue, may be confidential for 18 months or more after filing and can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use, sale or importation of our product candidates or future products. If a

patent holder believes the manufacture, use, sale, offer for sale or importation of one of our product candidates or future products infringes its patent, the patent holder may sue us even if we have licensed other patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our licensed patent portfolio may therefore have no deterrent effect.

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, importation 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 future products or the manufacture or use of our future products.

Third parties may assert infringement claims against us based on existing intellectual property rights and intellectual property rights that may be granted in the future. If we were to challenge the validity of an issued U.S. patent in court, such as an issued U.S. patent of potential relevance to some of our product candidates or future products or manufacture or methods of use, we would need to overcome a statutory presumption of validity that attaches to every U.S. patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent's claims. There is no assurance that a court would find in our favor on questions of infringement or validity.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. If we are found, or believe there is a risk we may be found, to infringe a third-party's intellectual property rights, we could be required or may choose to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any such 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. Without such a license, 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 future products or force us to cease some of our business operations, which could materially harm our business. Alternatively, we may need to redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. If we lose a foreign patent lawsuit alleging our infringement of a competitor's patents, we could be prevented from marketing our therapeutics in one or more foreign countries and/or be required to pay monetary damages for infringement or royalties in order to continue marketing. Claims that we have misappropriated the confidential information, trade secrets or other intellectual property of third parties could have a similar negative impact on our business. Any of these outcomes would have a materially adverse effect on our business.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our future products or processes. Patent litigation is costly and time-consuming, and some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. We may not have sufficient resources to bring these actions to a successful conclusion. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts, adversely affect our ability to raise additional funds, and could limit our ability to continue our operations.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position may be harmed.

In addition to the protection afforded by patents, we rely upon unpatented trade secret protection, unpatented know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our contractors, collaborators, scientific advisors, employees and consultants and invention assignment agreements with our consultants and employees. We may not be able to prevent the unauthorized disclosure or use of our technical know-how or other trade secrets by the parties to these agreements, however, despite the existence generally of confidentiality agreements and other contractual restrictions. Monitoring unauthorized uses and disclosures is difficult and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the contractors, collaborators, scientific advisors, employees and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. As a result, we could lose our trade secrets. Enforcing a claim that a third-party illegally obtained and is using our trade secrets, like patent litigation, is expensive and time-consuming and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing or unwilling to protect trade secrets.

Our trade secrets could otherwise become known or be independently discovered by our competitors. Competitors could purchase our product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If our trade secrets are not adequately protected or sufficient to provide an advantage over our competitors, our competitive position could be adversely affected, as could our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets.

Obtaining and maintaining 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.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and foreign patent agencies over the lifetime of the patent. While an unintentional lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in premature abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our product candidates, which would have a material adverse effect on our business.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property 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 in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. 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. Further, licensing partners may not prosecute patents in certain jurisdictions in which we may obtain commercial rights, thereby precluding the possibility of later obtaining patent protection in these countries. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States. Competitors may use our technologies in

jurisdictions where we have not obtained patent protection to develop their own products and may also export infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Most of our in-licensed patent families are pending in major pharmaceutical markets including the United States, Canada, Europe, Japan, Korea, and China, as well as other jurisdictions; we will not be able to enforce the patent in any jurisdictions in which the application has not been filed. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and we or our licensor may be unable to predict and may fail to seek patent protection in jurisdictions in which protection may ultimately be desired.

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, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, 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. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs 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. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents, trademarks, copyrights 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 and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. The outcome following legal assertions of invalidity and unenforceability is unpredictable. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. 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 during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail

in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Changes in patent law in the United States and in ex-U.S. jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain.

Past or future patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. For example, in March 2013, under the Leahy-Smith America Invents Act, or America Invents Act, the United States moved from a "first to invent" to a "first-inventor-to-file" patent system. Under a "first-inventor-to-file" system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention regardless of whether another inventor had made the invention earlier. The America Invents Act includes a number of other significant changes to U.S. patent law, including provisions that affect the way patent applications are prosecuted, redefine prior art and establish a new post-grant review system. The effects of these changes are currently unclear as the USPTO continues to promulgate new regulations and procedures in connection with the America Invents Act and many of the substantive changes to patent law, including the "first-inventor-to-file" provisions, only became effective in March 2013. In addition, the courts have yet to address many of these provisions and the applicability of the act and new regulations on the specific patents discussed in this filing have not been determined and would need to be reviewed. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

Additionally, recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, in the case, *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.,* the U.S. Supreme Court held that certain claims to DNA molecules are not eligible for patent protection. We cannot predict how future decisions by the courts, the U.S. Congress or the USPTO may impact the value of our patents. Any similar adverse changes in the patent laws of other jurisdictions could also have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to claims asserting that our employees, consultants, advisors or collaborators have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of or other rights to what we regard as our own or licensed intellectual property.

Many of our employees, consultants or advisors, and the employees, consultants or advisors of our licensors, are currently, or were previously, employed at or affiliated with universities, hospitals or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Moreover, some of our licensors, and our or our licensors' employees, consultants or advisors are or have been affiliated or have a contractual relationship with multiple institutions and companies including our competitors and may have or have had an obligation to them. Such institutions and companies could challenge our license rights or our licensors' intellectual property ownership rights. Litigation may be necessary to defend against these claims and we may be obligated to indemnify our employees, consultants, advisors or collaborators in certain instances. If we fail in 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 defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or 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, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting our product candidates might expire before or shortly after we or our partners commercialize those candidates. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

If we do not obtain patent term extension for any product candidates we may develop, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments.

The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent per product may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, even if we were to seek a patent term extension, it may not be granted because of, for example, the failure to exercise due diligence during the testing phase or regulatory review process, the failure to apply within applicable deadlines, the failure to apply prior to expiration of relevant patents, or any other failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations, and prospects could be materially harmed.

Some of the intellectual property rights that we have in-licensed were generated through the use of U.S. government fundingand are thereforesubject to federal regulations such as "march-in" rights, certain reporting requirements, and a preference for U.S. based companies. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with ex-U.S. manufacturers.

Some of the intellectual property rights we have in-licensed were generated through the use of U.S. government funding and are therefore subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act, and implementing regulations. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us or our licensors to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register

the intellectual property within specified time limits. These time limits have recently been changed by regulation, and may change in the future. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with ex-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

Risks Related to Government Regulation

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

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

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial when and if they achieve regulatory approval. Therefore, we expect that coverage and reimbursement by government and private payors will be essential for most patients to be able to afford these treatments. Accordingly, sales of any of our product candidates will depend substantially, both domestically 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 will be reimbursed by government authorities, private health coverage insurers and other third-party payors. 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. However, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Further, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. 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.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the EU, 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 product candidates 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. 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 certain third-party payors, such as health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market.

In addition to CMS and private payors, professional organizations such as the American Medical Association 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. Even if favorable coverage and reimbursement status is attained for one or more products for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Fast Track Designation by the FDA may not lead to a faster development or regulatory review or approval process.

We have obtained Fast Track Designation for PBGM01 for the treatment of GM1 gangliosidosis, for PBFT02 for the treatment of FTD-GRN and for PBKR03 for the treatment of Krabbe disease. We may seek Fast Track Designation for one or more of our other product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the product sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so 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 if we do receive Fast Track Designation, 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.

If we decide to seek Orphan Drug Designation for some of our product candidates, we may be unsuccessful or may be unable to maintain the benefits associated with Orphan Drug Designation, including the potential for supplemental market exclusivity.

We have obtained Orphan Drug Designations for PBGM01 for the treatment of GM1 gangliosidosis, for PBFT02 for the treatment of FTD-GRN and for PBKR03 for the treatment of Krabbe disease. We have sought and may continue to seek Orphan Drug Designation for one or more of our other product candidates, and we may be unsuccessful. Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is a drug 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, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, Orphan Drug Designation entitles a party to financial incentives such as tax advantages and user-fee waivers. Opportunities for grant funding toward clinical trial costs may also be available for clinical trials of drugs for rare diseases, regardless of whether the drugs are designated for the orphan use. In addition, if a product that has Orphan Drug Designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to

market the same product for the same indication for seven years, except in limited circumstances. For large molecule drugs, including gene therapies, sameness is determined based on the principal molecular structural features of a product. As applied to gene therapies, the FDA has recently issued final guidance in which it stated it generally intends to consider certain key features, such as the transgenes expressed by the gene therapy and the vectors used to deliver the transgene, to be principal molecular structural features. With regard to vectors, the FDA generally intends to consider whether two vectors from the same viral class are the same or different on a case-by-case basis. The FDA does not intend to consider minor differences between transgenes and vectors to be different principal molecular structural features. When two gene therapy products express the same transgene and have or use the same vector, determining whether two gene therapies are the same drug may also depend on additional features of the final gene therapy product, such as regulatory elements and the cell type that is transduced (for genetically modified cells). In such cases, FDA generally intends to determine whether two gene therapy products are different on a case-by-case basis.

Although we have obtained Orphan Drug Designation for our clinical product candidates, and even if we obtain Orphan Drug Designation for additional product candidates in specific indications, we may not be the first to obtain marketing approval of these product candidates for the orphan-designated indication due to the uncertainties associated with developing pharmaceutical products. If a competitor with a product that is determined by the FDA to be the same as one of our product candidates obtains marketing approval before us for the same indication we are pursuing and obtains orphan drug exclusivity, our product candidate may not be approved until the period of exclusivity ends unless we are able to demonstrate that our product candidate is clinically superior. Even after obtaining approval, we may be limited in our ability to market our product. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. 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 principal molecular structural features can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve the same drug with the same principal molecular structural features for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan Drug Designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process. In addition, while we may seek Orphan Drug Designation for some of our product candidates, we may never receive such designations. Similarly, the European Commission may also designate a product as an orphan drug under certain circumstances, and we have received Orphan designation for PBGM01 and PBKR03 from the European Commission.

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

Under the Rare Pediatric Disease Priority Review Voucher program, upon the approval of a qualifying BLA for the treatment of a rare pediatric disease, the sponsor of such an application would be eligible for a rare pediatric disease priority review voucher that can be used to obtain priority review for a subsequent BLA or NDA. If a product candidate is designated before September 30, 2024, it is eligible to receive a voucher if it is approved before September 30, 2026. While we have obtained Rare Pediatric Disease Designation for PBGM01 for the treatment of GM1 gangliosidosis and PBKR03 for the treatment of Krabbe disease, it is uncertain whether either product candidate will be approved by September 30, 2026. If approval is not obtained by then, we would not be in a position to obtain a priority review voucher, unless Congress further reauthorizes the program beyond the current sunset date in September 2024. Additionally, designation of a drug for a rare pediatric disease does not guarantee that a BLA will meet the eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Finally, a Rare Pediatric Disease Designation does not lead to faster development or regulatory review of the product or increase the likelihood that it will receive marketing approval.

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

Our product candidates and the activities associated with their development and potential 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, cGMPs, 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 and requirements regarding the distribution of samples to physicians and recordkeeping.

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

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

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

- refusal to permit the import or export of our product candidates;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

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

Our product candidates for which we intend to seek approval may face competition from biosimilars approved through an abbreviated regulatory pathway

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the ACA, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA. The BPCIA created an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as interchangeable based on its similarity to an existing reference product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product is approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty.

We believe that if any of our product candidates is approved as a biological product under a BLA, it should qualify for the 12-year period of exclusivity. However, there is a risk that the FDA will not consider any of our product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Additionally, this period of regulatory exclusivity does not apply to companies pursuing regulatory approval via their own traditional BLA, rather than via the abbreviated pathway. Moreover, an interchangeable biosimilar, once approved, may be substituted under existing law for any one of our reference products in a way that is similar to traditional generic substitution; any non-interchangeable biosimilar products may also be substituted by a health care provider but, under existing law, will not be automatically substituted at the pharmacy. The extent of the impact of such substituion will depend on a number of marketplace and regulatory factors that are still developing. Finally, there has been public discussion of potentially decreasing the period of exclusivity from the current 12 years. If such a change were to be enacted, our product candidates, if approved, could have a shorter period of exclusivity than anticipated.

Enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may affect the prices we may set. The full effect of recent United States healthcare reform and other changes in the healthcare industry, laws, and regulations and in healthcare spending is currently unknown, and the reform and other changes may adversely affect our business model.

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, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval. The commercial potential for our products, if any, could be affected by changes in healthcare spending and policy in the United States and abroad. New laws, regulations, or judicial decisions or new interpretations of existing laws, regulations, or decisions, related to healthcare availability, the method of delivery, or payment for healthcare products and services could adversely affect our business, operations, and financial condition, if and when we are able to obtain marketing approval and commercialize our products. For example, the ACA was enacted in 2010 with a goal, among others, of reducing the cost of healthcare and substantially changing the way healthcare is financed by both government and private insurers. The ACA, among other things, expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program, imposed a significant annual, nondeductible fee on companies that manufacture or import certain branded prescription drug products, and enacted substantial provisions affecting compliance, which may affect our business practices with healthcare practitioners.

There have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs in general and the cost of pharmaceuticals in particular. These initiatives recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which, among other things, will allow HHS to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D (excluding drugs and biologics that are designated and approved for only one rare disease or condition), although only high-expenditure single-source biologics that have been approved for at least 11 years (7 years for drugs) 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 representing a significant discount from average prices to wholesalers and direct purchasers. Beginning in October 2022 for Medicare Part D and January 2023 for Medicare Part B, penalizes drug manufacturers that increase prices of Medicare Part D and Part B 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 through a newly established manufacturer discount program. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. 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. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. Thus, it is unclear how the IRA will be implemented but will likely have a significant impact on the pharmaceutical industry.

Further, at the U.S. state level, legislatures are increasingly enacting laws and implementing regulations designed to control pharmaceutical and biological product pricing, including price or reimbursement constraints, discount requirements, marketing cost disclosure and price increase transparency reporting, and programs designed to encourage importation from other countries and bulk purchasing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services or otherwise negatively impact our business model. Our operations and 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 penalties including criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers 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 providers, 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 may include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward 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 federal healthcare programs such as Medicare and Medicaid;
- federal false claims laws, including the federal False Claims Act, imposes criminal and civil penalties, including through 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, among other things, knowingly and willfully executing or attempting to execute 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, or HITECH, Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, on certain types of people and entities with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payment Sunshine Act requires applicable manufacturers of covered drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), physician assistants, certain types of advanced practice nurses, and teaching hospitals, as well as certain ownership and investment interests held by physicians and their immediate family, which includes annual data collection and reporting obligations; 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 state laws require reporting of certain 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, disgorgement, oversight monitoring, contractual damages, reputational harm, diminished profits and future earnings, 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.

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

We may be required to expand our manufacturing, development and regulatory capabilities in the future, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We may be required to expand our manufacturing, development and regulatory capabilities in the future, which could result in growth to the number of our employees and the scope of our operations, particularly in the areas of manufacturing and clinical strategy, and growing our capability to conduct clinical trials. We may not be able to effectively manage the expansion of our operations in the future 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.

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

We are highly dependent on the research and development, clinical and business development expertise of our management, scientific and clinical team. We also benefit from the research expertise of Dr. Wilson, our Chief Scientific Advisor. Although we have entered into a consulting agreement with Dr. Wilson, he may terminate his relationship with us at any time. Although we have entered into employment letter agreements or employment agreements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and manufacturing strategy. Our consultants and advisors 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.

Recruiting and retaining qualified scientific, clinical, manufacturing and, if needed, 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, gain regulatory approval of and commercialize drugs, particularly within the gene therapy space. 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. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

Further, the reductions in workforce announced in March 2022 and November 2022 may also make retention of our current personnel both more important and more challenging. These workforce reductions resulted in the loss of longer-term employees, the loss of institutional knowledge and expertise and the reallocation and combination of certain roles and responsibilities across the organization, all of which could adversely affect our operations. Given the complexity of our business, we must continue to implement and improve our managerial, operational and financial systems, manage our facilities and continue to recruit and retain qualified personnel. Given the complexity of our business, we must continue to implement and improve our managerial, operational and financial systems, manage our facilities and continue to recruit and retain qualified personnel.

Further, we recently underwent a leadership transition, which may be viewed negatively by employees, investors and/or our strategic partners. Moreover, any attrition associated with this transition could significantly delay or prevent the achievement of product development and commercialization, and other business objectives, and adversely impact our stock price.

Our internal computer systems, or those of our third-party collaborators or other contractors, may fail or suffer security breaches and cyber attacks, which could result in a material disruption of our development programs.

We believe that we take reasonable steps that are designed to protect the security, integrity and confidentiality of the information we collect, use, store, and disclose, but inadvertent or unauthorized data access may occur despite our efforts. For example, our system protections may be ineffective or inadequate, or we could be impacted by software bugs or other technical malfunctions, as well as employee error or malfeasance. Additionally, privacy and data protection laws are evolving, and it is possible that these laws may be interpreted and applied in a manner that is inconsistent with our data handling safeguards and practices that could result in fines, lawsuits, and other penalties, and significant changes to our or our third-party partners business practices and products and service offerings. To the extent that the measures we or our third-party business partners have taken prove to be insufficient or inadequate, we may become subject to litigation, breach notification obligations, or regulatory or administrative sanctions, which could result in significant fines, penalties, damages, harm to our reputation or loss of patients. While we have not experienced any material losses as a result of any system failure, accident or security breach to date, we have been the subject of certain phishing attempts in the past. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. Additionally, a party who circumvents our security measures could, among other effects, appropriate patient information or other proprietary data, cause interruptions in our operations, or expose patients to hacks, viruses, and other disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, insurance coverage to compensate for any losses associated with such events may not be adequate to cover all potential losses. The development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated.

To the extent that any disruption, security breach, or cyber-attack were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed. Depending on the nature of the information compromised, in the event of a data breach or other unauthorized access to our patient data, we may also have obligations to notify patients and regulators about the incident, and we may need to provide some form of remedy, such as a subscription to credit monitoring services, pay significant fines to one or more regulators, or pay compensation in connection with a class-action settlement (including under the new private right of action under the California Consumer Privacy Act of 2018, or the CCPA, which is expected to increase security breach litigation). Such breach notification laws continue to evolve and may be inconsistent from one jurisdiction to another. Complying with these obligations could cause us to incur substantial costs and could increase negative publicity surrounding any incident that compromises patient data. Additionally, 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 an adverse effect on our business, reputation, operating results, and financial condition.

Our ability to utilize our net operating loss carryforwards may be subject to limitation.

As of December 31, 2022, we had federal net operating loss, or NOL, carryforwards of $199.3 million. $0.3 million of the federal NOLs will begin to expire in 2037, if not used prior to that date, and the remainder will carryforward indefinitely.

As of December 31, 2022, we had state NOL carryforwards of $199.3 million, which will begin to expire in 2037, and expire through 2042.

As of December 31, 2022, we had local NOL carryforwards of $180.9 million, which will begin to expire in 2023, and expire through 2042.

To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any. Under legislative changes made by U.S. federal tax legislation, commonly referred to as the Tax Cuts and Jobs Act, or the TCJA, U.S. federal net operating losses incurred in 2018 and in future years may be carried forward indefinitely, but the ability to utilize such federal net operating losses to offset taxable income is limited to 80% of our taxable income before the deduction for such net operating loss carryovers. It is uncertain if and to what extent various states will conform to the TCJA.

Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the IRC, 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 NOLs and other pre-change tax attributes (such as research tax credits) to offset its post-change income and post-change liability may be limited. We have not undertaken a Section 382 study, and it is possible that we have previously undergone one or more ownership changes so that our use of net operating losses is subject to limitation. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership. As a result, if we earn net taxable income, our ability to use our pre-change NOLs to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. 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.

U.S. federal income tax reform and changes in other tax laws could adversely affect us.

Tax laws are being re-examined and evaluated globally, and tax authorities are increasingly scrutinizing the tax positions of companies. Changes in tax laws and regulations in federal, state, local, and foreign jurisdictions could have material adverse impacts on our business, cash flows, operating results, or financial condition, and could materially affect our tax obligations and effective tax rate. For example, U.S. tax legislation enacted on December 22, 2017, informally titled the Tax Cuts and Jobs Act, or the Tax Cuts and Jobs Act, significantly reformed the Internal Revenue Code of 1986, as amended, or the Code. This legislation, among other things, included changes to U.S. federal tax rates, imposed significant additional limitations on the deductibility of interest and the use of net operating losses generated in tax years beginning after December 31, 2017 and allowed for the expensing of capital expenditures. The Tax Cuts and Jobs Act is unclear in many respects and could be subject to potential amendments and technical corrections, as well as interpretations and implementing regulations by the Treasury and the Internal Revenue Service, or IRS, any of which could lessen or increase certain adverse impacts of the legislation. In addition, in response to the COVID-19 pandemic, the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, was signed into law in March 2020, and subsequently in December 2020, the Continued Assistance for Unemployed Workers Act of 2020, or CARES Act II, was signed into law. The CARES Act and CARES Act II modify certain of the changes made by the Tax Cuts and Jobs Act. Changes in corporate tax rates, the realization of net deferred tax assets, and the deductibility of expenses under the Tax Cuts and Jobs Act, as amended by the CARES Act and CARES Act II, or future tax reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges in the current or future taxable years, and could increase our future U.S. tax expense. The foregoing items, as well as any other future changes in tax laws, could have a material adverse effect on our business, operating results and financial condition. In addition, it is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act, as amended by the CARES Act and CARES Act II, or any newly enacted federal tax legislation. Changes in tax laws or regulations in the

various tax jurisdictions we are subject to that are applied adversely to us or our clients could increase the costs of our products and harm our business.

Additionally, we use our best judgment in attempting to quantify and reserve for our tax obligations. However, a challenge by a taxing authority, a limitation on our ability to utilize tax benefits such as carryforwards or tax credits, or a deviation from other tax-related assumptions could have a material adverse effect on our business, results of operations, or financial condition.

Our employees, principal investigators, CROs and consultants may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of FDA and ex-U.S. regulators, provide accurate information to the FDA and ex-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but 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 comply with these laws 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, including the imposition of significant fines or other sanctions.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidates that we may develop.

We will face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and will face an even greater risk if we commercialize any of our product candidates. If we cannot successfully defend ourselves against claims that our product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates that we may develop;
- injury to our reputation and significant negative media attention;
- initiation of investigations by regulators;
- withdrawal of clinical trial participants;
- significant time and expenses to defend the related litigation;
- diversion of management and scientific resources from our business operations;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any product candidates that we may develop.

We currently hold limited product liability insurance coverage. We will need to purchase additional product liability insurance coverage as we expand our clinical trials, and if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. A successful product liability claim or series of claims brought against us, could decrease our cash and adversely affect our business and financial condition.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We can face criminal liability and other serious consequences for violations that can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors, and other partners from authorizing, promising, offering, or providing, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties for clinical trials outside of the United States, to sell our products abroad once we enter a commercialization phase, and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other partners, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

Risks Related to Our Common Stock

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

Our stock price has been and is likely to continue to be volatile. The stock market in general and the market for 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:

- results of preclinical studies or clinical trials of our product candidates or those of our competitors;
- unanticipated or serious safety concerns related to the use of any of our product candidates;
- adverse regulatory decisions, including failure to receive regulatory approval for any of our product candidates;
- the success of competitive drugs or technologies;
- regulatory or legal developments in the United States and other countries applicable to our product candidates;
- the size and growth of our prospective patient populations;
- developments concerning our collaborators, our external manufacturers or in-house manufacturing capabilities;
- inability to obtain adequate product supply for any product candidate for preclinical studies, clinical trials or future commercial sale or inability to do so at acceptable prices;
- 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 drugs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts or publications of research reports about us or our industry;
- 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 biotechnology sector;

- our cash position or the announcement or expectation of additional financing efforts;
- the ongoing COVID-19 pandemic could adversely impact our business, including our clinical trials and clinical trial operations;
- general economic, industry and market conditions, including rising interest rates and inflation;
- general economic uncertainty and capital markets disruptions, which has been substantially impacted by geopolitical instability due to the ongoing military conflict in Ukraine; and
- other factors, including those described in this "Risk Factors" section, many of which are beyond our control.

Our executive officers, directors, principal stockholders and their affiliates exercise significant influence over our company, which will limit your ability to influence corporate matters and could delay or prevent a change in corporate control.

As of December 31, 2022, our executive officers, directors, beneficial owners of 5% or more of our capital stock and their respective affiliates beneficially owned shares representing a substantial portion of our capital stock.

This group of stockholders has the ability to control us through this ownership position and may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may feel are in your best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with your interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

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

We have never declared or paid any cash dividends on our common stock and do not currently intend to do so for the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will be limited to the appreciation of stock. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in value of the stock. We cannot guarantee you that shares of our common stock will appreciate in value or even maintain the price at which our stockholders have purchased their shares.

If we fail to establish and maintain proper and effective internal control over financial reporting in the future, our ability to produce accurate and timely financial statements could be impaired, which could harm our operating results, investors' views of us and, as a result, the value of our common stock.

Pursuant to Section 404 of the Sarbanes-Oxley Act, we are required to furnish a report by our management on our internal control over financial reporting within our Form 10-K. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that will need to be frequently evaluated. Section 404 of the Sarbanes-Oxley Act requires public companies to conduct an annual review and evaluation of their internal controls and attestations of the effectiveness of internal controls, however, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. Our failure to maintain the effectiveness of our internal controls in accordance with the requirements of the Sarbanes-Oxley Act could have a material adverse effect on our business.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 financial statements. In addition, if we are not able to continue to meet these requirements, we may not be able to remain listed on The Nasdaq Stock Market LLC, or Nasdaq.

As we grow, we expect to hire additional personnel and may utilize external temporary resources to implement, document and modify policies and procedures to maintain effective internal controls. However, it is possible that we may identify deficiencies and weaknesses in our internal controls. If material weaknesses or deficiencies in our internal controls exist and go undetected or unremediated, our financial statements could contain material misstatements that, when discovered in the future, could cause us to fail to meet our future reporting obligations and cause the price of our common stock to decline.

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

As a public company, particularly after we are no longer an "emerging growth company," we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and Nasdaq have imposed 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 increase our legal and financial compliance costs and will make some activities more time-consuming and costly. We are an "emerging growth company" and "smaller reporting company," and the reduced disclosure requirements applicable to emerging growth companies and smaller reporting companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earlier of (i) the last day of the fiscal year in which we have total annual gross revenue of $1.235 billion or more; (ii) December 31, 2025; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the last business day of our most recently completed second fiscal quarter. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- being permitted to present 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 in this Form 10-K;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We may choose to take advantage of some, but not all, of the available exemptions. Even after we no longer qualify as an emerging growth company, we may still qualify as a smaller reporting company, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have

elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will not be subject to the same adoption timelines for new or revised accounting standards as other public companies that are not emerging growth companies.

We are also a "smaller reporting company," meaning that the market value of our stock held by non-affiliates is less than $700.0 million and our annual revenue is less than $100.0 million during the most recently completed fiscal year. We will continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than $250.0 million or (ii) our annual revenue is less than $100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700.0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

The exclusive forum provisions in our restated certificate of incorporation and amended and restated bylaws may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims.

Our restated certificate of incorporation, to the fullest extent permitted by law, provides that the Court of Chancery of the State of Delaware will be the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, or the DGCL, our restated certificate of incorporation, or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. This exclusive forum provision does not apply to suits brought to enforce a duty or liability created by the Securities Exchange Act of 1934, as amended, or the Exchange Act. It could apply, however, to a suit that falls within one or more of the categories enumerated in the exclusive forum provision and asserts claims under the Securities Act, inasmuch as Section 22 of the Securities Act, creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rule and regulations thereunder. There is uncertainty as to whether a court would enforce such provision with respect to claims under the Securities Act, and our stockholders will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder.

In March 2020, we amended and restated our restated bylaws to 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, or 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 a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provisions contained in our restated certificate of incorporation or amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, results of operations and financial condition.

In addition, Section 203 of the DGCL may discourage, delay or prevent a change in control of our company. Section 203 imposes certain restrictions on mergers, business combinations and other transactions between us and holders of 15% or more of our common stock.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, 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 restated certificate of incorporation and our restated 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 so that not all members of our board are elected at one time;
- permit only the board of directors to establish the number of directors and fill vacancies on the board;
- provide that directors may only be removed "for cause" and only with the approval of two-thirds of our stockholders;
- require super-majority voting to amend some provisions in our restated certificate of incorporation and restated bylaws;
- authorize the issuance of "blank check" preferred stock that our board could use to implement a stockholder rights plan, also known as a "poison pill";
- eliminate the ability of our stockholders to call special meetings of stockholders;
- prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders;
- prohibit cumulative voting; and
- establish advance notice requirements for nominations for election to our board or for proposing matters that can be acted upon by stockholders at annual stockholder meetings.

Moreover, we are governed by the provisions of Section 203 of the DGCL, 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.

General Risk Factors

We may be subject to securities litigation, which could result in substantial expenses and could divert management attention.

The market price of our common stock has been and may continue to be volatile. The stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to 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 analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. We do not have any control over the analysts or the content and opinions included in

their reports. If one or more of the analysts covering our business downgrade their evaluations of our stock, the trading price of our stock would likely decrease. Even if we do obtain analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

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

We maintain a large quantity of sensitive information, including confidential business and personal information in connection with the operation of our business, 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 constantly evolving laws can be subject to varying interpretations. In addition, states are constantly adopting new laws or amending existing laws, requiring attention to frequently changing regulatory requirements with inconsistent or conflicting standards.

California has enacted the CCPA, which became operative on January 1, 2020 and became enforceable by the California Attorney General on July 1, 2020. Additionally, in the California Privacy Rights Act, or CPRA, which expands upon the CCPA, became effective on January 1, 2023. The CCPA and CPRA require covered companies to, among other things, provide new disclosures to California users, and affords such users new privacy rights such as the ability to opt-out of certain sales of personal information and expanded rights to access and require deletion of their personal information, opt-out of certain personal information sharing, and receive detailed information about how their personal information is collected, used, and shared. The CCPA and CPRA provide for civil penalties for violations, as well as a private right of action for security breaches that may increase security breach litigation. Potential uncertainty surrounding the CCPA and CPRA may increase our compliance costs and potential liability, particularly in the event of a data breach, and could have a material adverse effect on our business, including how we use personal information, our financial condition, the results of our operations or prospects.

Other states have passed similar laws, and a number of other states are actively considering bills with similar laws. To the extent multiple state-level laws are later introduced, it may require costly and difficult efforts to achieve compliance with such laws that could expose us to fines and penalties for non-compliance.

In the European Economic Area, or the EEA, the General Data Protection Regulation or the GDPR, governs the collection, use, disclosure, transfer or other processing of personal data of European persons. Among other things, the GDPR imposes requirements regarding the security of personal data and notification of data processing obligations to the competent national data processing authorities, changes the lawful bases on which personal data can be processed, expands the definition of personal data and requires changes to informed consent practices, as well as more detailed notices for clinical trial subjects and investigators. In addition, the GDPR increases the scrutiny of transfers of personal data from clinical trial sites located in the EEA to the United States and other jurisdictions that the European Commission does not recognize as having "adequate" data protection laws (sometimes referred to as "third countries"), and imposes strict rules subject to substantial fines for breaches and violations (up to the greater of €20 million or 4% of our annual worldwide gross revenue). These obligations may be interpreted and applied in a manner that is inconsistent from one jurisdiction to another and may conflict with other requirements or our practices.

Additionally, in the United Kingdom, or U.K., the Data Protection Act contains provisions, including its own derogations, for how GDPR is applied in the U.K. We have to continue to comply with the GDPR and also the U.K.'s Data Protection Act, with each regime having the ability to fine up to the greater of €20 million (£17 million) or 4% of global turnover.

In 2020, the Court of Justice of the European Union, or CJEU, invalidated the European Union-United States, or E.U.-U.S., Privacy Shield (under which personal data could be transferred from the E.U. to U.S. entities that had self-certified under the Privacy Shield scheme), or Privacy Shield on the grounds that the Privacy Shield failed to offer adequate protections to E.U. personal data transferred to the United States. The Biden administration negotiated new privacy shield terms with EU regulators and signed an Executive Order in October 2022 directing the steps the United States will take to implement its commitments to the EU/US data privacy framework. The new proposed Privacy Shield terms are subject to further review by EU regulators and member states.

In addition, while the CJEU upheld the adequacy of the standard contractual clauses (a standard form of contract approved by the European Commission as an adequate personal data transfer mechanism, and potential alternative to the Privacy Shield), it made clear that reliance on them alone may not necessarily be sufficient in all circumstances. Use of the standard contractual clauses must now be assessed on a case by case basis, taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals. The use of standard contractual clauses for the transfer of personal data specifically to the United States remains under review by a number of European data protection supervisory authorities, along with those of some other E.U. member states. German and Irish supervisory authorities have indicated, and enforced in recent rulings, that the standard contractual clauses alone provide inadequate protection for E.U.-U.S. data transfers. Further, on June 4, 2021 the European Commission finalized new versions of the Standard Contractual Clauses, with the Implementing Decision now in effect as of June 27, 2021. To comply with the Implementing Decision and the new Standard Contractual Clauses, we may need to implement additional safeguards to further enhance the security of data transferred out of the EEA, conduct data transfer impact assessments, and review existing agreements which could increase our compliance costs, expose us to further regulatory scrutiny and liability, and adversely affect our business. The new standard contractual clauses apply only to the transfer of data outside of the EEA and/or Switzerland and not the United Kingdom, though the U.K.'s Information Commissioner's Officer launched a public consultation on its draft international data transfer agreement in August 2021, and subsequently issued a new international data transfer agreement and addendum which we are required to use under Article 46 of the UK GDPR when making restricted data transfers outside of the UK.

The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of the GDPR.

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. If we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations. Furthermore, the laws are not consistent, and compliance in the event of a widespread data breach is costly.

We generally seek to comply with industry standards and are subject to the terms of our privacy policies and privacy-related obligations to third parties. We strive to comply with all applicable laws, policies, legal obligations and industry codes of conduct relating to privacy and data protection to the extent possible. However, it is possible that these obligations may be interpreted and applied in a manner that is inconsistent from one jurisdiction to another and may conflict with other rules or our practices. Any failure or perceived failure by us, even if unfounded, to comply with applicable privacy and data security laws and regulations, our privacy policies, or our privacy-related obligations to users or other third parties, or any compromise of security that results in the unauthorized release or transfer of personal information or other sensitive data, may result in governmental enforcement actions, litigation, or public statements against us by consumer advocacy groups or others and could cause our users to lose trust in us, which would have an adverse effect on our reputation and business.

Any significant change to applicable laws, regulations or industry practices regarding the use or disclosure of our users' data, or regarding the manner in which the express or implied consent of users for the use and disclosure of such data is obtained – or in how these applicable laws, regulations or industry practices are interpreted and enforced by state, federal and international privacy regulators – could require us to modify our practices, possibly in a material manner, may subject us to regulatory enforcement actions and fines, and may limit our ability to operate using the data that was voluntarily shared with us.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. For example, the global financial crisis caused extreme volatility and disruptions in the capital and credit markets, and, in recent months, the global economy has been impacted by increasing interest rates and inflation. Likewise, the capital and credit markets may be adversely affected by the recent conflict between Russia and Ukraine, and the possibility of a wider European or global conflict, and global sanctions imposed in response thereto. A severe or prolonged economic downturn, such as the global financial crisis, could result in a variety of risks to our business, including, weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We or the third parties upon whom we depend 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 and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as our manufacturing facilities, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. In addition, the long-term effects of climate change on general economic conditions and the pharmaceutical industry in particular are unclear, and may heighten or intensify existing risk of natural disasters. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. 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.

Item 1B. ***Unresolved Staff Comments***

None

Item 2. ***Properties and Facilities***

Our principal executive office is located in Philadelphia, Pennsylvania, where we lease a total of approximately 37,000 square feet of office space, that we use for our administrative, research and development and other activities, which commenced in February 2021 and will expire in December 2031, subject to our option to extend the term of the lease by up to two additional five-year terms.

We also lease approximately 62,000 square feet of laboratory space at the Princeton West Innovation Campus in Hopewell, New Jersey. This lease has a 15-year term from the lease commencement date of March 2021. We have the option to extend the term of the lease by up to two additional five-year terms.

Item 3. ***Legal Proceedings***

From time to time, we may be involved in legal proceedings arising in the ordinary course of our business. We are not presently a party to any legal proceedings that, in the opinion of management, would have a material adverse effect on 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 for Common Stock

Our common stock has been listed on The Nasdaq Global Market under the symbol "PASG" since February 28, 2020. Prior to that there was no public trading market for our common stock.

Holders of Record

As of March 2, 2023, there were approximately 24 stockholders of record of our common stock. 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.

Dividend Policy

We currently intend to retain future earnings, if any, for use in operation of our business and to fund future growth. We have never declared or paid any cash dividends on our capital stock and do not anticipate paying any cash dividends in the foreseeable future. Payment of cash dividends, if any, in the future will be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Unregistered Sales of Equity Securities

None.

Use of Proceeds from Registered 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 the related notes and other financial information included elsewhere in this Form 10-K. Some of the information contained in this discussion and analysis contains forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in this Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described below.

Overview

We are a clinical stage genetic medicines company focused on developing transformative therapies for CNS disorders. Our vision is to fulfill the promise of gene therapy by developing groundbreaking therapies that transform the lives of patients with CNS diseases. The field of genetic medicine is rapidly expanding and we believe we have a differentiated approach to developing treatments for CNS disorders that enables us to select and advance product candidates with a higher probability of technical and regulatory success. We have entered into a strategic research collaboration with the Trustees of the University of Pennsylvania's, or Penn's, Gene Therapy Program, or GTP, headed by Dr. James Wilson, a leader in the genetic medicines field. We also leverage our close working relationship with Penn's Orphan Disease Center, or ODC, to develop historical and prospective comparable natural history patient profiles for comparison to participants in interventional trials. Through this collaboration we have assembled a deep portfolio of genetic medicine product candidates, for which we retain global rights, including our two lead clinical product candidates: PBGM01 for the treatment of GM1 gangliosidosis, or GM1, and PBFT02 for the treatment of frontotemporal dementia, or FTD, and two clinical stage product candidates for which, in order to reduce operating expenses, we have stopped further clinical development and are exploring strategic alternatives: PBKR03 for the treatment of Krabbe disease and PBML04 for metachromatic leukodystrophy, or MLD. We have two programs in the research stage: PBAL05 for amyotrophic lateral sclerosis, or ALS, and an unnamed program for Huntington's disease. We also have an exploratory research program for Temporal Lobe Epilepsy, or TLE.

We were incorporated in July 2017 under the laws of the State of Delaware. Since inception, we have devoted substantially all of our resources to acquiring and developing product and technology rights, conducting research and development, organizing and staffing our company, business planning and raising capital. We have incurred recurring losses, the majority of which are attributable to research and development activities, and negative cash flows from operations. Historically, we have funded our operations through the sale of convertible preferred stock and public offerings of common stock. Our net losses were $136.1 million and $185.4 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $492.4 million. Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures, and to a lesser extent, general and administrative expenditures. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of one or more of our current or future product candidates. We expect to continue to incur significant expenses and operating losses for the foreseeable future as we advance our product candidates through all stages of development and clinical trials and, ultimately, seek regulatory approval. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Our net losses may fluctuate significantly from quarter to quarter and year to year, depending on the timing of our clinical trials and our expenditures on other research and development activities.

We will need to raise substantial additional capital to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we plan to finance our operations through the sale of equity, debt financings or other capital sources, which may include collaborations with other companies or other strategic transactions. There are no assurances that we will be successful in obtaining an adequate level of financing as and when needed to finance our operations on terms acceptable to us or at all. Any failure to raise capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies. If we are unable to secure adequate additional funding, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more product candidates or delay our pursuit of potential in-licenses or acquisitions.

In March 2022, we announced a 13 percent reduction in workforce and plans to prioritize research and development programs to reduce operating expenses and to extend our cash runway. In November 2022, we announced a further 23 percent reduction in workforce and plans to prioritize research and development programs to reduce operating expenses and to extend our cash runway.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of $189.6 million. We expect our existing cash, cash equivalents and marketable securities, will enable us to fund our operating expenses and capital expenditure requirements into the first half of 2025.

Financial Operations Overview

License Agreement

University of Pennsylvania

We have a research, collaboration and licensing agreement, as amended, or the Penn Agreement, with Penn, for research and development collaborations and exclusive license rights to patents for certain products and technologies. Under the Penn Agreement, we have the obligation to fund certain research relating to the preclinical development of selected products in research programs as well as the new exploratory research program in non-rare and/or non-monogenic, or large, CNS indications, currently in TLE. We also fund discovery research conducted by Penn through August 2026 and will receive exclusive rights, subject to certain limitations, to technologies resulting from the discovery program for products developed with GTP, such as novel capsids, toxicity reduction technologies and delivery and formulation improvements. Our discovery research funding commitment is $5.0 million a year for five years, with quarterly payments of $1.3 million through June 2026. Under the Penn Agreement we have eight remaining options available to us to commence additional licensed programs for CNS indications until August 2026. If we were to exercise any of these remaining options, we would owe Penn a non-refundable aggregate fee of $1.0 million, with $0.5 million per product indication paid immediately and another $0.5 million fee owed upon a further developmental milestone.

The Penn Agreement requires that we make payments of up to (i) $16.5 million per product candidate for rare, monogenic disorders in aggregate and (ii) $39.0 million per product candidate in the aggregate arising from the exploratory program for large CNS indications, currently TLE and such other mutually agreed upon large CNS indications. Each payment will be due upon the achievement of specific development milestone events by such licensed product for a first indication, reduced development milestone payments for the second and third indications and no development milestone payments for subsequent indications. In addition, on a product-by-product basis, we are obligated to make up to $55.0 million in sales milestone payments on each licensed product based on annual sales of the licensed product in excess of defined thresholds.

Upon successful commercialization of a product using the licensed technology, we are obligated to pay to Penn, on a licensed product-by-licensed product and country-by-country basis, tiered royalties (subject to customary reductions) in the mid-single digits on annual worldwide net sales of such licensed product. In addition, we are obligated to pay to Penn a percentage of sublicensing income, ranging from the mid-single digits to low double digits, for sublicenses under the Penn Agreement. In addition, we will pay Penn a tiered transaction fee ranging from 1-2% of the net proceeds upon certain change of control events.

The Penn Agreement includes an exploratory research collaboration to identify targets and early product candidates in such large CNS indications. The exploratory research program is focused on discovering targets and novel gene therapy candidates for large CNS diseases, currently focused on TLE, and that can be expanded to other large CNS diseases upon mutual agreement. The initial term of the exploratory research program is 3 years, or until August 2024, which term can be extended by mutual agreement. During such term we will have an exclusive right of first negotiation to include additional targets to the exploratory research program in the agreed upon large CNS indications. Under the exploratory research program, we will have the right to further develop and commercialize any gene therapy product candidates specific for those selected targets within TLE (and any future large CNS indications that are mutually agreed upon) that arise from the exploratory research programs on substantially the same terms of the current Penn Agreement.

In November 2022, we agreed with GTP to not continue further advancement of our exploratory research program in AD.

Collaboration and Manufacturing and Supply Agreements

Catalent

In June 2019, we entered into a collaboration agreement, or the Collaboration Agreement, with Catalent Maryland, Inc., or Catalent. As part of the Collaboration Agreement, we paid Catalent an upfront fee for the commissioning, qualification, validation and equipping of a dedicated clean room suite, or the Clean Room Suite. We will pay an annual fee for five years for the exclusive use of the Clean Room Suite, which commenced in November 2020 upon its validation.

In April 2020, we entered into a development services and clinical supply agreement, or the Manufacturing and Supply Agreement, with Catalent to secure clinical scale manufacturing capacity for batches of active pharmaceutical ingredients for our gene therapy product candidates. The Manufacturing and Supply Agreement provides for a term of five years which period may be extended once, at our option, for an additional five year-period. The Collaboration Agreement continues to be in effect pursuant to its terms. Under the terms of the Manufacturing and Supply Agreement, Catalent has agreed to manufacture batches of drug product for our gene therapy product candidates at the Clean Room Suite provided for in the Collaboration Agreement. There is a minimum annual purchase commitment owed to Catalent for five years beginning in November 2020, subject to certain inflationary adjustments. We have the right to terminate the Manufacturing and Supply Agreement for convenience or other reasons specified in the Manufacturing and Supply Agreement upon prior written notice. If we terminate the Manufacturing and Supply Agreement, we will be obligated to pay an early termination fee to Catalent.

Under both the Collaboration Agreement and the Manufacturing and Supply Agreement, we have an annual minimum commitment of $10.6 million per year owed to Catalent for five years from November 2020, subject to certain inflationary adjustments.

Components of Results of Operations

Research and Development and Acquired In-Process Research and Development

Research and development expenses consist primarily of costs incurred in connection with the development of our product candidates. These expenses include:

- expenses incurred to conduct the necessary preclinical studies and clinical trials required to obtain regulatory approval, including payments to Penn for preclinical research and development;
- expenses incurred in obtaining technology licenses related to technology that has not reached technological feasibility and has no alternative future use, which are classified as acquired In-process research and development;
- personnel expenses, including salaries, benefits and share-based compensation expense for employees engaged in research and development functions;
- expenses related to funding research performed by third parties, including pursuant to agreements with clinical research organizations, or CROs, as well as investigative sites and consultants that conduct our preclinical studies and clinical trials;
- expenses incurred under agreements with contract manufacturing organizations, or CMOs, including the cost of acquiring and manufacturing preclinical study and clinical trial materials;
- expenses and fees paid to consultants who assist with research and development activities; and
- allocated expenses for facilities costs, including rent, utilities, depreciation and maintenance.

We track outsourced development expenses and other external research and development expenses to specific product candidates on a program-by-program basis, such as expenses incurred under our collaboration with Penn, fees paid to

CROs, CMOs and research laboratories in connection with our preclinical development, process development, manufacturing and clinical development activities. However, we do not track our internal research and development expenses on a program-by-program basis as they primarily relate to compensation and other expenses which are deployed across multiple projects under development.

Expenses incurred in obtaining technology licenses are expensed as acquired in-process research and development if the technology licensed has not reached technological feasibility and has no alternative future use.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development expenses than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials.

Given our reductions in workforce and prioritization of research and development programs, in order to reduce operating expenses, we expect our research and development expenses to remain consistent or decrease in the near future.

If our product candidate portfolio progresses into later-stage clinical trials, we expect that our research and development expenses will increase in the future to support our continued research and development activities and production of clinical supply.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel expenses, including salaries, benefits and share-based compensation expense, for employees and consultants in executive, finance, accounting, legal, information technology, commercial, quality, regulatory, operations and human resource functions. General and administrative expenses also include corporate facility costs, including rent, utilities, depreciation and maintenance, legal expenses related to intellectual property and corporate matters, insurance expense, and expenses for accounting and consulting services.

Given our recent reduction in workforce and prioritization of operating expenses, we expect our general and administrative expenses to remain consistent or decrease in the near future.

If our product candidate portfolio progresses into later-stage clinical trials, we expect that our general and administrative expenses will increase in the future to support our continued research and development activities, potential commercialization efforts, and increased expenses of operating as a public company. These increases will likely include increased expenses related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses. If any of our current or future product candidates obtain regulatory approval, we expect that we would incur significantly increased expenses associated with building a commercial sales and marketing team.

Interest Income, net

Interest income, net consists of interest earned on our cash equivalents and marketable securities, offset by amortization of premium and discount on our marketable securities.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

The following table sets forth our results of operations for the years ended December 31, 2022 and 2021.

(in thousands)	Year ended December 31, 2022	2021	Change
Operating expenses:			
Research and development	$ 86,053	$ 117,673	$ (31,620)
Acquired in-process research and development	3,000	8,000	(5,000)
General and administrative	49,341	60,056	(10,715)
Loss from operations	(138,394)	(185,729)	47,335
Interest income, net	2,269	343	1,926
Net loss	$ (136,125)	$ (185,386)	$ 49,261

Research and Development Expenses

Research and development expenses decreased by $31.6 million from $117.7 million for the year ended December 31, 2021 to $86.1 million for the year ended December 31, 2022. The decrease was primarily due to decreases of: $22.7 million and $3.5 million in expenses for clinical manufacturing and clinical operations, respectively, which relates to the timing of our clinical manufacturing and operational activities to support our clinical trials; $9.6 million in research and development expenses with Penn; and, $3.0 million in personnel-related and share-based compensation expense. We expect that expenses associated with Penn will continue to vary from period to period based on the status of our preclinical pipeline and the timing of preclinical work performed. These decreases were partially offset by an increase of $3.6 million in professional services and an increase of $3.6 million in facility and other expenses, primarily due to depreciation.

We track outsourced development, outsourced personnel expenses and other external research and development costs of specific programs. We do not track our internal research and development expenses on a program-by-program basis. Research and development expenses are summarized by program in the table below:

(in thousands)	Year ended December 31, 2022	2021
Program Specific Expenses		
PBGM01 (GM1)	$ 10,055	$ 16,871
PBFT02 (FTD-GRN)	10,133	15,982
PBKR03 (Krabbe)	8,527	18,022
PBML04 (MLD)	5,949	12,542
Other Programs and Discovery	10,695	10,529
Unallocated Internal Expenses		
Personnel-related (including share-based compensation)	31,940	34,956
Other	8,755	8,771
	$ 86,053	$ 117,673

Acquired In-Process Research and Development Expenses

Acquired in-process research and development expenses were $3.0 million for the year ended December 31, 2022 compared to $8.0 million for the year ended December 31, 2021. We incurred $3.0 million in fees related to the achievement of development milestones for dosing our first patients in PBFT02 for the treatment of FTD and PBKR03 for the treatment of Krabbe during the year ended December 31, 2022.

General and Administrative Expenses

General and administrative expenses decreased by $10.8 million from $60.1 million for the year ended December 31, 2021 to $49.3 million for the year ended December 31, 2022. The decrease was primarily due to decreases of $8.8 million in personnel-related and share-based compensation expense and a $4.4 million decrease in professional services and other expenses. These decreases were partially offset by an increase of $2.4 million in facility and other expenses.

Interest Income, net

Interest income, net was $2.3 million and $0.3 million for the years ended December 31, 2022 and 2021, respectively. Interest income is primarily attributable to interest income earned on our cash, cash equivalents and marketable securities, partially offset by amortization of premium and discount on our marketable securities and fees paid to our external asset manager.

Liquidity and Capital Resources

Overview

As of December 31, 2022, we had $189.6 million in cash, cash equivalents and marketable securities and had an accumulated deficit of $492.4 million. We expect our existing cash, cash equivalents and marketable securities will enable us to fund our operating expense and capital expenditures into the first half of 2025.

Funding Requirements

Our primary use of cash is to fund operating expenses, most significantly research and development expenditures. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable, accrued expenses and prepaid expenses.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products, we are unable to estimate the exact amount of our operating capital requirements. Our future funding requirements will depend on many factors, including, but not limited to:

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

We will need additional funds to meet operational needs and capital requirements for clinical trials, other research and development expenditures, and business development activities. We currently have no credit facility or committed sources of capital. Because of the numerous risks and uncertainties associated with the development and

commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated clinical studies.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, existing stockholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect existing stockholders' rights as common stockholders. 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 acquisitions or 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 drug candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed, we may be required to delay, limit, further reduce or terminate our research, product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

On March 5, 2021, we entered into a Sales Agreement, or the Sales Agreement, with Cowen and Company, LLC, or Cowen, pursuant to which we may, but are not obligated to, offer and sell, from time to time, shares of our common stock with an aggregate offering price up to $125.0 million through Cowen, as sales agent. No sales of common stock have been made pursuant to this Sales Agreement to date.

Cash Flows

The following table shows a summary of our cash flows for the periods indicated:

	Year ended December 31,	
(in thousands)	**2022**	**2021**
Cash provided by (used in) operating activities	$ (118,210)	$ (126,879)
Cash provided by (used in) investing activities	25,199	(45,814)
Cash provided by (used in) financing activities	(1,353)	166,656
Net increase (decrease) in cash and cash equivalents	$ (94,364)	$ (6,037)

Net Cash Used in Operating Activities

During the year ended December 31, 2022, we used $118.2 million of net cash in operating activities, primarily to fund our operations related to the development of our product candidates and related general and administrative support activities. Cash used in operating activities reflected our net loss of $136.1 million, which was partially offset by adjustments to reconcile net loss to net cash used in operating activities of $26.9 million related to acquired in-process research and development expense, share-based compensation, depreciation and amortization, amortization of premium and discount of marketable securities, net and amortization of operating lease ROU asset as well as a $9.0 million net decrease in cash flows resulting from changes in our operating assets and liabilities.

During the year ended December 31, 2021, we used $126.9 million of net cash in operating activities, primarily to fund our operations related to the development of our product candidates and related general and administrative support activities. Cash used in operating activities reflected our net loss of $185.4 million, which was partially offset by adjustments to reconcile net loss to net cash used in operating activities of $47.1 million related to acquired in-process research and development expense, share-based compensation, depreciation and amortization, amortization of premium and discount of marketable securities, net and changes in deferred rent as well as a $11.4 million net increase in cash flows resulting from changes in our operating assets and liabilities.

Net Cash From Investing Activities

During the year ended December 31, 2022, we purchased $157.8 million in marketable securities and had sales and maturities of $188.3 million in marketable securities. Additionally, we used $2.3 million for the purchase of property and equipment and we used $3.0 million to purchase technology rights from Penn.

During the year ended December 31, 2021, we purchased $202.5 million in marketable securities and had sales and maturities of $182.4 million in marketable securities. Additionally, we used $17.6 million for the purchase of property and equipment and we used $8.0 million to purchase technology rights from Penn.

Net Cash Used in Financing Activities

During the year ended December 31, 2022, we received $0.1 million from the exercise of stock options, received $0.3 million in proceeds from the issuance of common stock under the ESPP and paid $1.8 million for insurance premiums and insurance premium financing expenses under our short-term insurance premium financing arrangement.

During the year ended December 31, 2021, financing activities provided $165.8 million from the sale of our common stock, we received $0.9 million from the issuance of common stock under our employee stock purchase plan, we received $0.3 million from the exercise of stock options, partially offset by payments for offering costs of $0.3 million.

Contractual obligations and other commitments

We lease approximately 37,000 square feet of office space in Philadelphia, Pennsylvania. The lease will expire in December 2031. We have an option to extend the term of the lease by up to two additional five-year terms. The aggregate estimated rent payments due over the initial term of the lease is $11.8 million, with rent payments that began in 2022.

We lease approximately 62,000 square feet of laboratory space in Hopewell, NJ. The lease will expire in March 2036. The aggregate estimated rent payments due over the initial term of the lease is approximately $40.3 million, with rent payments that began in 2021.

Under both the Collaboration Agreement and the Manufacturing and Supply Agreement with Catalent, we have an annual minimum commitment of $10.6 million per year owed to Catalent through November 2025, subject to certain inflationary adjustments. We have the right to terminate the Manufacturing and Supply Agreement for convenience or other reasons specified in the Manufacturing and Supply Agreement upon prior written notice. If we terminate the Manufacturing and Supply Agreement, we will be obligated to pay an early termination fee to Catalent.

Under the Penn Agreement, we agreed to fund discovery research conducted by Penn for five years, which began in May 2020. Our funding commitment is $5.0 million a year through June 2026.

The contractual obligations and commitments above are associated with contracts that are enforceable and legally binding and that specify all significant terms, including fixed or minimum services to be used, fixed, minimum or variable price provisions, and the approximate timing of the actions under the contracts. Payments due upon cancellation consisting only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation are not included in the preceding table as the amount and timing of such payments are not known.

The contractual obligations and commitments above do not include any potential milestone or royalty payments that we may be required to make under the Penn Agreement.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses and share-based compensation. We base our estimates on historical experience, known trends and events, and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 3 to our annual financial statements included elsewhere in this Form 10-K, we believe the following accounting policy is the most critical to the judgments and estimates used in the preparation of our financial statements.

Research and Development Expenses

Research and development costs are expensed as incurred and consist primarily of expenses incurred with Penn, contract research organizations, contract manufacturing organizations, internal analytical and testing activities, and employee-related expenses, including salaries, benefits, and share-based compensation.

We make estimates of our external accrued research and development expenses, which primarily relates to activities performed by our contract research organizations and contract manufacturing organizations, as of each balance sheet date in our financial statements based on an estimate of progress to completion of specific tasks using facts and circumstances known to us at that time. We determine the estimates by reviewing contracts, vendor agreements and change orders, invoicing to date, reviewing vendor provided supporting documentation and through discussions with our internal personnel and external service providers as to the progress to completion of services and the agreed-upon fee to be paid for such services.

Actual costs and estimates of progress to completion of our contract research organizations and contract manufacturing organizations are uncertain, subject to risks and may change depending upon a number of factors, including our enrollment levels and status of our clinical trials, and timing of our manufacturing activities. Such estimates are uncertain given the level of visibility we have towards the activities of our contract research organizations and contract manufacturing organizations. If the actual timing of the performance of services or the level of effort varies from the estimate, we will adjust the accrual and related expenses accordingly.

Recent Accounting Pronouncements

See Note 3 to our financial statements found elsewhere in this Form 10-K for a description of recent accounting pronouncements applicable to our financial statements.

JOBS Act Accounting Election

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies.

We have elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We will remain an emerging growth company until the earliest of (1) the last day of our first fiscal year (a) in which we have total annual gross revenues of at least $1.235 billion, or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700.0 million as of the prior June 30th, (2) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period and (3) December 31, 2025.

We are also a "smaller reporting company," meaning that the market value of our stock held by non-affiliates is less than $700.0 million and our annual revenue is less than $100.0 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than $250.0 million or (ii) our annual revenue is less than $100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700.0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

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 $189.6 million in cash, cash equivalents and marketable securities, all of which was denominated in U.S. dollar assets, and consisting primarily of cash accounts in banking institutions and investments in money market funds, certificates of deposit, commercial paper, corporate bonds and investments in U.S. and non-U.S. treasury securities.

We are 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 financial statements.

Inflation may affect us by increasing our cost of labor, cost of external services, and cost of external goods and raw materials. We do not believe that inflation has had a material effect on our business, financial condition or results of operations for any period presented herein.

Item 8. Financial Statements and Supplementary Data

PASSAGE BIO, INC.

INDEX TO AUDITED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and Board of Directors
Passage Bio, Inc.:

Opinion on the Financial Statements

We have audited the accompanying balance sheets of Passage Bio, Inc. (the Company) as of December 31, 2022 and 2021, the related statements of operations and comprehensive loss, stockholders' equity, and cash flows for the years then ended, and the related notes (collectively, the financial statements). In our opinion, the 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 the years then ended, in conformity with U.S. generally accepted accounting principles.

Change in Accounting Principle

As discussed in Notes 1 and 3 to the financial statements, the Company has changed its method of accounting for leases as of January 1, 2022 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases (Topic 842)*.

Basis for Opinion

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

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

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

/s/ KPMG LLP

We have served as the Company's auditor since 2019.

Philadelphia, Pennsylvania
March 6, 2023

Passage Bio, Inc.
Balance Sheets

(in thousands, except share data)	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 34,601	$ 128,965
Marketable securities	155,009	186,808
Prepaid expenses and other current assets	926	1,726
Prepaid research and development	6,508	7,567
Total current assets	197,044	325,066
Property and equipment, net	22,515	23,806
Right of use assets - operating leases	19,723	-
Other assets	4,267	6,204
Total assets	$ 243,549	$ 355,076
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,065	$ 9,448
Accrued expenses and other current liabilities	11,011	20,050
Operating lease liabilities	3,275	-
Total current liabilities	18,351	29,498
Operating lease liabilities - noncurrent	23,832	-
Deferred rent	-	6,921
Total liabilities	42,183	36,419
Commitments and Contingencies (note 10)		
Stockholders' equity:		
Common stock, $0.0001 par value: 300,000,000 shares authorized; 54,614,690 shares issued and outstanding at December 31, 2022 and 54,244,996 shares issued and outstanding at December 31, 2021	5	5
Additional paid-in capital	694,733	675,346
Accumulated other comprehensive income (loss)	(966)	(413)
Accumulated deficit	(492,406)	(356,281)
Total stockholders' equity	201,366	318,657
Total liabilities and stockholders' equity	$ 243,549	$ 355,076

See accompanying notes to financial statements.

Passage Bio, Inc.
Statements of Operations and Comprehensive Loss

(in thousands, except share and per share data)	Year Ended December 31, 2022	2021
Operating expenses:		
Research and development	$ 86,053	$ 117,673
Acquired in-process research and development	3,000	8,000
General and administrative	49,341	60,056
Loss from operations	(138,394)	(185,729)
Interest income, net	2,269	343
Net loss	$ (136,125)	$ (185,386)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (2.50)	$ (3.48)
Weighted average common shares outstanding, basic and diluted	54,429,023	53,343,959
Comprehensive loss:		
Net loss	$ (136,125)	$ (185,386)
Unrealized gain (loss) on marketable securities	(553)	(401)
Comprehensive loss	$ (136,678)	$ (185,787)

See accompanying notes to financial statements.

Passage Bio, Inc.
Statements of Stockholders' Equity
(in thousands, except share data)

	Stockholders' equity					
	Common stock		Additional	Accumulated other	Accumulated	
(in thousands, except share data)	Shares	Amount	paid-in capital	comprehensive income (loss)	deficit	Total
Balance at January 1, 2021	45,614,807	$ 4	$ 475,617	$ (12)	$ (170,895)	$ 304,714
Vesting of early exercise option awards	302,277	-	45	-	-	45
Exercise of stock options and vesting of restricted stock units	186,787	-	301	-	-	301
Issuance of shares in connection with employee stock purchase plan	91,125	-	887	-	-	887
Sale of common stock, net of issuance costs of $669	8,050,000	1	165,805	-	-	165,806
Unrealized gain (loss) on marketable securities	-	-	-	(401)	-	(401)
Share-based compensation expense	-	-	32,691	-	-	32,691
Net loss	-	-	-	-	(185,386)	(185,386)
Balance at December 31, 2021	54,244,996	$ 5	$ 675,346	$ (413)	$ (356,281)	$ 318,657

	Stockholders' equity					
	Common stock		Additional	Accumulated other	Accumulated	
(in thousands, except share data)	Shares	Amount	paid-in capital	comprehensive income (loss)	deficit	Total
Balance at January 1, 2022	54,244,996	$ 5	$ 675,346	$ (413)	$ (356,281)	$ 318,657
Exercise of stock options and vesting of restricted stock units	165,223	-	129	-	-	129
Issuance of shares in connection with employee stock purchase plan	204,471	-	304	-	-	304
Unrealized gain (loss) on marketable securities	-	-	-	(553)	-	(553)
Share-based compensation expense	-	-	18,954	-	-	18,954
Net loss	-	-	-	-	(136,125)	(136,125)
Balance at December 31, 2022	54,614,690	$ 5	$ 694,733	$ (966)	$ (492,406)	$ 201,366

See accompanying notes to financial statements.

Passage Bio, Inc.
Statements of Cash Flows

(in thousands)	Year Ended December 31, 2022	2021
Cash flows used in operating activities:		
Net loss	$ (136,125)	$ (185,386)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:		
Acquired in-process research and development	3,000	8,000
Depreciation and amortization	3,679	1,543
Share-based compensation	18,954	32,691
Amortization of premium and discount on marketable securities, net	773	2,778
Deferred rent	-	2,075
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets, and other assets	2,737	1,842
Prepaid research and development	1,059	3,394
Right of use assets and operating lease liabilities	463	-
Accounts payable	(5,412)	2,201
Accrued expenses and other current liabilities	(7,338)	3,983
Net cash provided by (used in) operating activities	(118,210)	(126,879)
Cash flows provided by (used in) investing activities:		
Purchases of marketable securities	(157,835)	(202,546)
Sales or maturities of marketable securities	188,308	182,374
Purchases of technology licenses	(3,000)	(8,000)
Purchases of property and equipment	(2,274)	(17,642)
Net cash provided by (used in) investing activities	25,199	(45,814)
Cash flows provided by (used in) financing activities:		
Proceeds from issuance of common stock, net of offering costs	-	165,806
Payment of offering costs	-	(338)
Proceeds from the exercise of stock options	129	301
Proceeds from the issuance of common stock under employee stock purchase plan	304	887
Payments for insurance premium financing	(1,786)	-
Net cash provided by (used in) financing activities	(1,353)	166,656
Net increase (decrease) in cash and cash equivalents	(94,364)	(6,037)
Cash and cash equivalents at beginning of year	128,965	135,002
Cash and cash equivalents at end of year	$ 34,601	$ 128,965
Supplemental disclosure of non-cash investing and financing activities:		
Unrealized gain (loss) on marketable securities	$ (553)	$ (401)
Property and equipment in deferred rent	$ -	$ 2,769
Property and equipment in accounts payable and accrued expenses and other current liabilities	$ 114	$ 2,143
Vesting of early exercise option awards	$ -	$ 45
Right of use assets recognized upon the adoption of Topic 842	$ (20,375)	$ -
Operating lease liabilities recognized upon the adoption of Topic 842	$ 27,296	$ -

See accompanying notes to financial statements.

Passage Bio, Inc.
Notes to Financial Statements

1. Nature of Operations

Passage Bio, Inc., or the Company, a Delaware corporation incorporated in July 2017, is a clinical stage genetic medicines company focused on developing transformative therapies for central nervous system, or CNS disorders, with limited or no approved treatment options. The Company has a strategic research collaboration with the Trustees of the University of Pennsylvania's, or Penn, Gene Therapy Program, or GTP. Under this collaboration, GTP conducts discovery and preclinical activities enabling Investigational New Drug, or IND, applications and the Company conducts all clinical development, manufacturing, regulatory strategy, and commercialization activities under the agreement.

Through this collaboration, the Company has assembled a portfolio of genetic medicine product candidates, including two lead clinical product candidates: PBGM01 for the treatment of GM1 gangliosidosis, or GM1, and PBFT02 for the treatment of frontotemporal dementia, or FTD. The Company also has a collaboration agreement and a development services and clinical supply agreement with Catalent Maryland, Inc., or Catalent, for clinical scale manufacturing requirements.

2. Risks and Liquidity

The Company has incurred recurring losses and negative cash flows from operations since inception and had an accumulated deficit of $492.4 million as of December 31, 2022. The Company anticipates incurring additional losses until such time, if ever, that it can generate significant sales of its product candidates currently in development. Substantial additional capital will be needed by the Company to fund its operations and to develop its product candidates.

In January 2021, the Company closed a follow-on public offering in which the Company issued and sold 8,050,000 shares of its common stock at a public offering price of $22.00 per share for net proceeds of $165.8 million after deducting underwriting discounts, commissions and other offering expenses.

The Company's operations have consisted primarily of conducting preclinical studies, developing licensed technology, conducting clinical trials and manufacturing clinical supply to support clinical trials. The Company faces risks associated with early-stage biotechnology companies whose product candidates are in development. Product candidates currently under development will require significant additional research and development efforts and establishing manufacturing capacity and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital for the Company to complete its research and development, achieve its research and development objectives, defend its intellectual property rights, and recruit and retain skilled personnel, and key members of management. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

The Company plans to seek additional funding through public or private equity offerings, debt financings, other collaborations, strategic alliances and licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into strategic alliances or other arrangements on favorable terms, or at all. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. If the Company is unable to obtain funding or prospects of funding are unfavorable, the Company could be required to further delay, reduce or eliminate research and development programs, product portfolio expansion or future commercialization efforts, which could adversely affect its business prospects.

In March 2022 and November 2022, the Company reduced its workforce and prioritized research and development programs to reduce operating expenses and to extend its cash runway.

In accordance with Accounting Standards Update, or ASU, No. 2014-15*, Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern*, the Company has evaluated whether there are certain 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 that the financial statements are issued. As of the issuance date of these financial statements, the Company expects that its cash, cash equivalents and marketable debt securities will be sufficient to fund its forecasted operating expenses and capital expenditure requirements for at least the next twelve months from the issuance date of these financial statements.

3. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying financial statements have been prepared in accordance with generally accepted accounting principles in the United States, or GAAP. Any reference in these notes to applicable guidance is meant to refer to GAAP as found in the Accounting Standards Codification, or ASC, and Accounting Standards Updates promulgated by the Financial Accounting Standards Board, or FASB.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and contingent liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates.

Estimates and assumptions are periodically reviewed and the effects of the revisions are reflected in the accompanying financial statements in the period they are determined to be necessary.

Fair Value of Financial Instruments

Management believes that the carrying amounts of the Company's financial instruments, including cash equivalents, prepaid expenses, and accounts payable, approximate fair value due to the short-term nature of those instruments.

Concentration of credit risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash, cash equivalents, and marketable securities. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts and believes it is not exposed to significant risk on its cash, cash equivalents, and marketable securities.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one segment.

Cash and cash equivalents

The Company considers all highly-liquid investments that have maturities of three months or less when acquired to be cash equivalents. Cash equivalents as of December 31, 2022 consisted of money market funds and commercial paper. Cash consists of cash deposits at banking institutions.

Marketable securities

The Company classifies its marketable securities as available-for-sale, which include commercial paper, certificates of deposit, corporate debt securities, and United States, or U.S., government debt securities with original maturities of greater than three months. These securities are carried at fair market value, with unrealized gains and losses reported in comprehensive loss and accumulated other comprehensive income (loss) within stockholders' equity. Gains or losses on marketable securities sold are recognized as a component of other income, net in the statement of operations and comprehensive loss on the specific identification method. All marketable securities are available for use, as needed, to fund operations and therefore, the Company classifies all marketable securities as current assets within the balance sheet.

Property and Equipment, net

Property and equipment consists of laboratory equipment, office equipment, computer hardware and software, furniture and leasehold improvements and are recorded at cost. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed as incurred. Property and equipment are depreciated on a straight-line basis over their estimated useful lives. The Company estimates useful life on an asset by asset basis, which generally consists of three years for computer hardware and software, five years for office equipment, five years for laboratory equipment and seven years for furniture and fixtures. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

The Company reviews long-lived assets, such as property and equipment, for impairment when events or changes in circumstances indicate the carrying amount of the assets may not be recoverable. If circumstances require a long-lived asset to be tested for possible impairment, recoverability is measured by comparison of the carrying amount of the assets to estimated future undiscounted cash flows that the assets are expected to generate. If the carrying amount of an asset exceeds its estimated future cash flows, then impairment expense is recognized for the amount by which the carrying amount of the asset exceeds the fair value of the asset. For the years ended December 31, 2022, and 2021, no impairment expenses were recognized.

Share-based compensation

The Company measures share-based awards at grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards. The Company's share-based compensation consists of restricted stock units, or RSUs, and options to purchase common stock, or stock option awards.

The Company uses the Black-Scholes option pricing model to value its stock option awards.

Estimating the fair value of stock option awards requires the input of assumptions, including, the expected term of stock options and stock price volatility. The Company accounts for forfeitures for stock option awards as they occur. The assumptions used in estimating the fair value of share-based awards represent management's estimate and involve inherent uncertainties and the application of management's judgment. As a result, if factors change and management uses different assumptions, share-based compensation expense could be materially different for future awards.

The expected term of the stock options is estimated using the "simplified method," as the Company has limited historical information from which to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock option grants. The simplified method is the midpoint between the vesting period and the contractual term of the option.

For stock price volatility, the Company uses a composite of comparable public company data as a basis for its expected volatility to calculate the fair value of option grants. The selection of comparable public company data requires the application of management's judgement.

The Company accounts for forfeitures for stock option awards as they occur.

Research and Development

Research and development costs are expensed as incurred and consist primarily of expenses incurred with Penn, contract research organizations, contract manufacturing organizations, internal analytical and testing activities, and employee-related expenses, including salaries, benefits, and share-based compensation. Management makes estimates of the Company's external accrued research and development expenses, which primarily relates to contract research organizations and contract manufacturing organizations, as of each balance sheet date in the Company's financial statements based on an estimate of progress to completion of specific tasks using facts and circumstances known to the Company at that time. The Company determines the estimates by reviewing contracts, vendor agreements and change orders, and through discussions with our internal clinical personnel and external service providers as to the progress to completion of services and the agreed-upon fee to be paid for such services. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company will adjust the accrual and related expenses accordingly.

Acquired In-Process Research and Development

Fees paid to obtain research and development technology licenses are recognized as acquired in-process research and development expense if the research and development technology licensed has not reached technological feasibility and has no alternative future use. For the years ended December 31, 2022, and 2021, all fees paid to obtain technology licenses were recognized as acquired in-process research and development expense.

Income Taxes

Income taxes are accounted for under the asset-and-liability method as required by FASB ASC Topic 740, *Income Taxes* (ASC 740). Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period corresponding to the enactment date. Under ASC 740, a valuation allowance is required when it is more likely than not all or some portion of the deferred tax assets will not be realized through generating sufficient future taxable income.

FASB ASC Subtopic 740-10, Accounting for Uncertainty of Income Taxes, (ASC 740-10) defines the criterion an individual tax position must meet for any part of the benefit of the tax position to be recognized in financial statements prepared in conformity with GAAP. The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not such tax position will be sustained on examination by the taxing authorities, based solely on the technical merits of the respective tax position. The tax benefits recognized in the financial statements from such a tax position should be measured based on the largest benefit having a greater than 50% likelihood of being realized upon ultimate settlement with the tax authority. In accordance with the disclosure requirements of ASC 740-10, the Company's policy on statement of operations classification of interest and penalties related to income tax obligations is to include such items as part of total interest income, net.

Net Loss Per Share

Basic net loss per share of common stock is computed by dividing net loss by the weighted-average number of shares of common stock outstanding during each period. Diluted loss per share of common stock includes the effect, if any, from the potential exercise or conversion of securities, such as stock options, which would result in the issuance of incremental shares of common stock. For diluted net loss per share, the weighted-average number of shares of common

stock is the same for basic net loss per share due to the fact that when a net loss exists, dilutive securities are not included in the calculation as the impact is anti-dilutive.

The following potentially dilutive securities have been excluded from the computation of diluted weighted-average shares of common stock outstanding, as they would be anti-dilutive:

	Year Ended December 31,	
	2022	2021
Stock options	11,411,390	9,416,998
Unvested restricted stock units	1,229,166	290,500
Employee stock purchase plan	26,680	33,753
	12,667,236	9,741,251

Recently Adopted Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)*, or ASU 2016-02, which requires a lessee to record a right-of-use asset and a corresponding lease liability on the balance sheet for all leases with terms longer than 12 months. The Company adopted ASU 2016-02 on January 1, 2022 using the modified retrospective transition method and elected the following transition practical expedients: (i) to not reassess lease identification, lease classification and initial indirect costs related to those leases entered into prior to the adoption of Topic 842; and (ii) to not separate lease and non-lease components for the Company's operating lease portfolio. The Company recorded an operating lease right-of-use asset and lease liability of $20.4 million and $27.3 million respectively, related to the adoption of the Topic 842. See note 9 for further details.

Recently Issued Accounting Pronouncements

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments-Credit Losses: Measurement of Credit Losses on Financial Instruments*, or ASU 2016-13, which replaces the incurred loss impairment methodology under current U.S. GAAP with a methodology that reflects expected credit losses and requires consideration of a broader range of reasonable and supportable information to inform credit loss estimates. ASU 2016-13 was subsequently updated by ASU No. 2019-04, *Codification Improvements to Topic 326, Financial Instruments—Credit Losses, Topic 815, Derivatives and Hedging, and Topic 825, Financial Instruments*, to clarify that entities should include recoveries when estimating the allowance for credit losses. This guidance is effective for the Company starting in fiscal year 2023. The Company does not expect that the adoption of ASU 2016-13 will have a material impact on its financial statements.

4. Cash, cash equivalents and marketable securities

The following table provides details regarding the Company's portfolio of cash and cash equivalents:

(in thousands)	Cost or Amortized cost	Unrealized gains	Unrealized losses	Fair value
December 31, 2022:				
Cash accounts in banking institutions	$ 7,532	$ -	$ -	$ 7,532
Money market funds	24,578	-	-	24,578
Commercial paper	2,491	-	-	2,491
Total	$ 34,601	$ -	$ -	$ 34,601
December 31, 2021:				
Cash accounts in banking institutions	$ 44,549	$ -	$ -	$ 44,549
Money market funds	84,416	-	-	84,416
Commercial paper	-	-	-	-
Total	$ 128,965	$ -	$ -	$ 128,965

The following table provides details regarding the Company's portfolio of marketable securities:

(in thousands)	Amortized cost	Unrealized gains	Unrealized losses	Fair value
December 31, 2022:				
Certificates of deposit	$ 28,197	$ 6	$ (92)	$ 28,111
Commercial paper	58,572	12	(72)	58,512
Corporate debt securities	67,206	1	(786)	66,421
U.S. government securities	2,000	-	(35)	1,965
Total	$ 155,975	$ 19	$ (985)	$ 155,009
December 31, 2021:				
Certificates of deposit	$ 5,296	$ -	$ -	$ 5,296
Commercial paper	26,503	4	(4)	26,503
Corporate debt securities	145,577	10	(418)	145,169
U.S. government securities	1,996	-	(8)	1,988
Non-U.S. government securities	7,849	4	(1)	7,852
Total	$ 187,221	$ 18	$ (431)	$ 186,808

The contractual maturities of our marketable securities as of December 31, 2022, are as follows:

(in thousands)	Amortized Cost	Fair Value
Due within one year	$ 144,583	$ 143,779
Due after one year through five years	11,392	11,230
Total	$ 155,975	$ 155,009

5. Fair Value of Financial Instruments

Fair value is the price that could be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. Fair value determination in accordance with applicable accounting guidance requires that a number of significant judgments be made. Additionally, fair value is used on a nonrecurring basis to evaluate assets for impairment or as required for disclosure purposes by applicable accounting guidance on disclosures about fair value of financial instruments. Depending on the nature of the assets and liabilities, various valuation techniques and assumptions are used when estimating fair value. The carrying amounts of certain of the Company's financial instruments, including prepaid expense and accounts payable are shown at cost, which approximates fair value due to the short-term nature of these instruments. The Company follows the provisions of FASB ASC Topic 820, *Fair Value Measurement*, for financial assets and liabilities measured on a recurring basis. The guidance requires fair value measurements be classified and disclosed in one of the following three categories:

- *Level 1:* Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities.

- *Level 2:* Quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liabilities.

- *Level 3:* Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

The following fair value hierarchy table presents information about the Company's assets measured at fair value on a recurring basis. Included within cash and cash equivalents on the balance sheet, but excluded from the fair value hierarchy table, are cash deposits held at financial institutions:

	Fair value measurement at reporting date using		
(in thousands)	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
December 31, 2022:			
Assets			
Cash equivalents:			
Money market funds	$ 24,578	$ -	$ -
Commercial paper	-	2,491	-
Total cash equivalents	24,578	2,491	-
Marketable securities:			
Certificates of deposit	-	28,111	-
Commercial paper	-	58,512	-
Corporate debt securities	-	66,421	-
U.S. government securities	-	1,965	-
Total marketable securities	-	155,009	-
Total financial assets	$ 24,578	$ 157,500	$ -
December 31, 2021:			
Assets			
Cash equivalents:			
Money market funds	$ 84,416	$ -	$ -
Commercial paper	-	-	-
Total cash equivalents	84,416	-	-
Marketable securities:			
Certificates of deposit	-	5,296	-
Commercial paper	-	26,503	-
Corporate debt securities	-	145,169	-
U.S. government securities	-	1,988	-
Non-U.S. government securities	-	7,852	-
Total marketable securities	-	186,808	-
Total financial assets	$ 84,416	$ 186,808	$ -

6. Property and Equipment, net

Property and Equipment, net, consist of the following:

(in thousands)	December 31, 2022	December 31, 2021
Laboratory equipment	$ 9,972	$ 8,916
Office equipment	601	621
Computer hardware and software	1,090	1,028
Furniture and fixtures	1,208	1,487
Leasehold improvements	13,506	13,409
Construction in progress	1,291	822
Total property and equipment	27,668	26,283
Accumulated depreciation and amortization	(5,153)	(2,477)
	$ 22,515	$ 23,806

Depreciation expense was $3.7 million and $1.5 million for the years ended December 31, 2022 and 2021, respectively.

7. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following:

(in thousands)	December 31, 2022	December 31, 2021
Professional fees	$ 602	$ 877
Compensation and related benefits	8,446	10,014
Research and development	1,878	8,498
Property and equipment	85	161
Other	-	500
	$ 11,011	$ 20,050

8. Severance

In March 2022 and November 2022, the Company announced workforce reductions and that it has prioritized certain research and development programs to reduce operating expenses and to extend its cash runway. In connection with these announcements, the Company reduced headcount by approximately 13% and 23% in March 2022 and November 2022, respectively.

In accordance with ASC 420, *Exit and Disposal Activities,* the Company recorded severance and termination-related costs of $3.8 million in general and administrative expenses and $2.3 million in research and development expenses for the year ended December 31, 2022.

As of December 31, 2022, $2.1 million of severance and termination-related costs were unpaid and recognized in the balance sheet within Accrued expenses and other current liabilities.

9. Leases

On January 1, 2022, the Company adopted ASU No. 2016-02, *Leases*, using a modified retrospective approach and recorded operating lease right-of-use, or ROU, assets and operating lease liabilities of $20.4 million and $27.3 million, respectively, related to the Company's Lease Agreement and Laboratory Lease Agreement, or collectively, the Leases, which are each defined below. The Company elected the package of practical expedients available under ASU No. 2016-

02 and as such, did not reassess any of the Company's existing or expired contracts or any other agreements that were previously concluded to not contain a lease for the following practical expedient guidance: (1) whether the arrangement is or contains a lease, (2) lease classification and (3) whether previously capitalized costs continue to qualify as initial direct costs. In addition, the Company applied the accounting policy election to not separate lease and non-lease components and the accounting policy election to not apply the recognition requirement under ASU No. 2016-02 to leases with a term of twelve months or less.

The Company was not required to record a cumulative effect adjustment upon adoption as the Company did not capitalize any material initial direct costs nor were any contracts reassessed leading to changes in the terms or contractual payments of historical arrangements that would impact expense recognition, however, the Company eliminated $3.2 million of deferred rent liabilities and $3.8 million of tenant improvement allowances as of January 1, 2022 related to the Leases as these liabilities are reflected in the operating lease ROU assets. The Company used incremental borrowing rates, or IBRs, of 9.0% and 10.0% to discount the operating lease liabilities for the Lease Agreement and the Laboratory Lease Agreement, respectively. The Company's IBRs were quoted by an unrelated third-party lender and reflect a collateralized borrowing with similar terms and amounts as the Leases.

The Company is party to a lease agreement for office space, or the Lease Agreement, in Philadelphia, Pennsylvania. The Lease Agreement commenced in February 2021 and is expected to expire in December 2031. The Company has an option to extend the term of the Lease Agreement by up to two five-year terms. This option to extend was not recognized as part of the Company's measurement of the ROU asset and operating lease liability as of December 31, 2022. The landlord provided the Company with a tenant improvement allowance of $2.8 million, for which the related expenditures were paid directly by the landlord.

The Company is also party to a lease agreement for laboratory space, or the Laboratory Lease Agreement, in Hopewell, New Jersey. The laboratory is initially focused on state-of-the-art analytical capabilities, assay development and validation, and clinical product testing to support both viral vector manufacturing and clinical development. The Laboratory Lease Agreement commenced in March 2021 and is expected to expire in February 2036. The Company has an option to extend the term of the Laboratory Lease Agreement by up to two five-year terms. This option to extend was not recognized as part of the Company's measurement of the ROU asset and operating lease liability as of December 31, 2022. The landlord provided the Company with a tenant improvement allowance of $1.3 million in connection with the Laboratory Lease Agreement, for which the related expenditures were paid by the Company and will be reimbursed by the landlord. As of December 31, 2022, $0.1 million of reimbursements were unpaid by the landlord and recorded within other current assets.

The following table summarizes the Company's operating leases:

($ in thousands)	Year Ended December 31, 2022
Operating lease cost	$ 3,316
Cash paid for amounts included in the measurement of operating cash flows from operating leases	$ 2,853
Weighted-average discount rate	9.7%
Weighted-average remaining lease term (years)	12.2

The following table summarizes future minimum lease payments under the Company's operating lease agreements:

(in thousands)		
2023	$	3,455
2024		3,553
2025		3,654
2026		3,757
2027		3,864
Thereafter		29,679
Total undiscounted lease payments		47,962
Less: imputed interest		(20,855)
Total lease liabilities	$	27,107

10. Commitments and Contingencies

Amended and Restated Research, Collaboration and License Arrangement with Penn

The Company has a research, collaboration and licensing agreement with Penn, as amended, or the Penn Agreement, for research and development collaborations and exclusive license rights to patents for certain products and technologies. Under the Penn Agreement, the Company has obligations to fund certain research relating to the preclinical development of selected products in research programs as well as the exploratory research program in non-rare and/or non-monogenic, or large CNS indications, currently TLE. In addition, the Company will fund discovery research conducted by Penn through August 3, 2026 and will receive exclusive rights, subject to certain limitations, to technologies resulting from the discovery research for the Company's products developed with GTP, such as novel capsids, toxicity reduction technologies and delivery and formulation improvements. This funding commitment for the discovery research is $5.0 million annually, paid in quarterly increments of $1.3 million through June 2026.

The Penn Agreement includes an exploratory research program focused on discovering targets and novel gene therapy candidates for large CNS indications, currently focused on TLE, and can be expanded to other large CNS diseases upon mutual agreement. The initial term of the exploratory research program is until August 2024, which term can be extended by mutual agreement. During such term, the Company will have an exclusive right of first negotiation to include additional targets to the exploratory research program within the agreed upon large CNS indications. Under the exploratory research program, the Company will have the right to further develop and commercialize any gene therapy product candidates specific for those selected targets within TLE (and any future large CNS diseases that are mutually agreed upon) that may arise from the exploratory research programs on substantially the same terms of the current Penn Agreement.

Under the Penn Agreement, the Company has eight remaining options available to commence additional licensed programs for CNS indications and has until August 3, 2026, to exercise these options. If the Company were to exercise any of these options, it would owe Penn a non-refundable upfront fee of $1.0 million per product indication, with $0.5 million due upfront and another $0.5 million fee owed upon a further developmental milestone. The Company has the obligation to fund certain research relating to the preclinical development of each licensed program.

The Penn Agreement requires that the Company make payments of up to (i) $16.5 million per product candidate for rare, monogenic disorders in the aggregate and (ii) $39.0 million per product candidate in the aggregate arising from the exploratory program for large CNS indications, currently for TLE. Each payment will be due upon the achievement of specific development milestone events by such licensed product for a first indication, reduced development milestone payments for the second and third indications and no development milestone payments for subsequent indications. In addition, on a product-by-product basis, the Company is obligated to make up to $55.0 million in sales milestone payments on each licensed product based on annual sales of the licensed product in excess of defined thresholds.

Upon successful commercialization of a product using the licensed technology, the Company is obligated to pay to Penn, on a licensed product-by-licensed product and country-by-country basis, tiered royalties (subject to customary reductions) in the mid-single digits on annual worldwide net sales of such licensed product. In addition, the Company is obligated to pay to Penn a percentage of sublicensing income, ranging from the mid-single digits to low double digits, for sublicenses under the Penn Agreement. The agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the later of (i) the expiration of the last valid claim of the licensed patent rights that covers the exploitation of such licensed product in such country, and (ii) the expiration of the royalty period. In addition, the Company will pay a tiered transaction fee of 1-2% of the net proceeds upon certain change of control events.

During the year ended December 31, 2022, the Company made payments under the Penn Agreement of $3.0 million related to the achievement of development milestones for dosing our first patients in PBFT02 for the treatment of FTD and PBKR03 for the treatment of Krabbe disease, which were recognized as in-process research and development expense. During the year ended December 31, 2021, the Company made payments under the Penn Agreement of $1.5 million related to the achievement of a development milestone, $1.5 million related to option exercises under the Penn Agreement, and a $5.0 million payment related to the August 2021 amendment, which were recognized as in-process research and development expense.

Catalent Agreements

In June 2019, the Company entered into a collaboration agreement, or the Collaboration Agreement, with Catalent. As part of the Collaboration Agreement, the Company will pay an annual fee for five years ending in 2025 for the use of the Clean Room Suite.

In April 2020, the Company entered into a development services and clinical supply agreement, or the Manufacturing and Supply Agreement, with Catalent to secure clinical scale manufacturing capacity for batches of active pharmaceutical ingredients for the Company's gene therapy product candidates. The Manufacturing and Supply Agreement confirms the terms contemplated by the Collaboration Agreement. The Collaboration Agreement continues to be in effect pursuant to its terms.

Under the terms of the Manufacturing and Supply Agreement, Catalent has agreed to manufacture batches of drug product for the Company's gene therapy product candidates at the Clean Room Suite at a Catalent facility provided for in the Collaboration Agreement. The Manufacturing and Supply Agreement provides for a term of five years which period may be extended once, at the Company's option, for an additional five-year period. The Manufacturing and Supply Agreement also includes minimum annual purchase commitments.

The Company has the right to terminate the Manufacturing and Supply Agreement for convenience or other reasons specified in the Manufacturing and Supply Agreement upon prior written notice. If the Company terminates the Manufacturing and Supply Agreement, it will be obligated to pay an early termination fee to Catalent.

Under both the Collaboration Agreement and the Manufacturing and Supply Agreement, the Company has an annual minimum commitment of $10.6 million per year owed to Catalent for five years from the validation of the Clean Room, subject to certain inflationary adjustments. For the years ended December 31, 2022 and 2021, the Company paid amounts in excess of the minimum commitment.

Employment Agreements

The Company has entered into employment agreements with key personnel providing for compensation and, in certain circumstances, severance and acceleration of vesting in stock-based compensation awards, as described in the respective employment agreements.

11. Common Stock

In January 2021, the Company closed a follow-on public offering in which the Company issued and sold 8,050,000 shares of its common stock, which included shares sold pursuant to an option granted to the underwriters to purchase additional shares, at a public offering price of $22.00 per share for net proceeds of $165.8 million after deducting underwriting discounts, commissions and other offering expenses.

On March 5, 2021, the Company entered into a Sales Agreement, or the Sales Agreement, with Cowen and Company, LLC, or Cowen, pursuant to which the Company may, but are not obligated to, offer and sell, from time to time, shares of the Company's common stock with an aggregate offering price up to $125.0 million through Cowen, as sales agent. No sales of common stock have been made pursuant to this Sales Agreement to date.

12. Share-Based Compensation

Equity Incentive Plan

The Company has three equity incentive plans: the 2018 Equity Incentive Plan, as amended, or the 2018 Plan, the 2020 Equity Incentive Plan, or the Incentive Plan, and the 2021 Equity Inducement Plan, or the Inducement Plan. New awards can only be granted under the Incentive Plan and the Inducement Plan.

The total number of shares authorized under the Incentive Plan as of December 31, 2022 was 10,370,926. Additionally, any awards previously issued under our 2018 Plan which were forfeited become available for issuance under the Incentive Plan. As of December 31, 2022, 3,880,210 shares were available for future grants under our Incentive Plan. The number of shares of the Company's common stock that may be issued pursuant to rights granted under the Incentive Plan shall automatically increase on January 1st of each year, commencing on January 1, 2021 and continue for ten years, in an amount equal to five percent of the total number of shares of the Company's common stock outstanding on December 31st of the preceding calendar year, subject to the discretion of the board of directors or compensation committee to determine a lesser number of shares shall be added for such year. As a result, the number of shares reserved for issuance under the Incentive Plan increased by 2,730,735 and 2,712,249 shares in January 2023 and 2022, respectively.

The Incentive Plan provides for the granting of common stock, incentive stock options, nonqualified stock options, restricted stock awards, and/or stock appreciation rights to employees, directors, and other persons, as determined by the Company's board of directors. The Company's stock options awarded to date under the Incentive Plan vest based on a requisite service period, generally over four-year periods, and have a term of ten years.

The Inducement Plan was approved by the Company's board of directors in July 2021. The total number of shares authorized under the Inducement Plan as of December 31, 2022 was 2,000,000, as a result of an increase to the shares authorized for issuance in February 2022. Of this amount, 384,167 shares were available for future grants as of December 31, 2022. The Inducement Plan provides for the granting of nonqualified stock options and restricted stock awards to employees hired by the Company, as determined by the Company's board of directors. The Company's stock options awarded to date under the Inducement Plan vest based on requisite service period and have a term of ten years. The Company's restricted stock units awarded to date under the Inducement Plan vest based on requisite service period and have a term based on each award agreement.

The Company measures share-based awards at their grant-date fair value and records compensation expense on a straight-line basis over the vesting period of the awards. The Company recorded share-based compensation expense in the following expense categories in its accompanying statements of operations for the period presented:

	Year Ended December 31,	
(in thousands)	2022	2021
Research and development	$ 8,278	$ 15,432
General and administrative	10,676	17,259
	$ 18,954	$ 32,691

During the year ended December 31, 2022, the Company modified certain awards and recognized $0.4 million related to the modifications, all of which was recognized in general & administrative expense. The terms of such modifications included, on an awards-by-award basis, acceleration of the vesting period and extensions of the post-employment period to exercise.

During the year ended December 31, 2021, the Company modified certain awards and recognized $7.4 million related to the modifications, $6.1 million of which was recognized in research and development expense and $1.3 million was recognized in general and administrative expense. The terms of such modifications included, on an awards-by-award basis, acceleration of the vesting period and extensions of the post-employment period to exercise.

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

	Number of shares	Weighted average exercise price per share	Weighted average remaining contractual term (years)
Outstanding at January 1, 2022	9,416,998	$ 13.72	8.6
Granted	6,609,441	3.09	
Exercised	(126,056)	1.02	
Forfeited	(4,488,993)	10.41	
Outstanding at December 31, 2022	11,411,390	$ 9.01	7.1
Vested and Exercisable at December 31, 2022	6,074,955	$ 11.55	5.3
Vested or expected to vest at December 31, 2022	11,411,390	$ 9.01	7.1

The weighted-average grant date fair value of options granted was $2.33 and $12.75 for the years ended December 31, 2022 and 2021, respectively.

The aggregate intrinsic value of options exercised was $0.2 and $1.3 million and during the year ended December 31, 2022 and 2021, respectively.

The aggregate intrinsic value of options outstanding as of December 31, 2022 was $0.1 million and the aggregate intrinsic value of options exercisable as of December 31, 2022 was de minimus.

As of December 31, 2022, the total unrecognized compensation expense related to unvested stock option awards was $24.1 million, which the Company expects to recognize over a weighted-average period of 2.4 years.

The 2018 Plan and 2020 Plan provide certain holders of stock options an election to early exercise prior to vesting. The Company has the right to repurchase early exercised options without transferring any appreciation in the value of the underlying shares to the employee if the employee terminates employment before the end of the original vesting period.

The repurchase price is the lesser of the original exercise price or the then fair value of the Company's common stock. As of December 31, 2022, 113,932 options to purchase common stock are unvested, but exercisable, under early exercise provisions.

The fair value of each option was estimated on the date of grant using the weighted average assumptions in the table below:

	Year Ended December 31,	
	2022	2021
Expected volatility	92.5 %	99.0 %
Risk-free interest rate	2.8 %	0.9 %
Expected term	5.9 years	6.0 years
Expected dividend yield	-	-

Restricted Stock Units

The Company issues restricted stock units, or RSUs, to employees that vest over periods as determined by the board of directors. Any unvested shares are forfeited upon termination of services. The fair value price of the RSUs is equal to the fair market value of the Company's common stock on the date of grant. Compensation expense is recognized on a straight-line basis over the vesting period of the RSUs.

The following table summarizes activity related to RSU awards during the year ended December 31, 2022:

	Number of shares		Weighted average grant date fair value
Unvested balance at January 1, 2022	290,500	$	14.78
Granted	1,171,500	$	1.97
Vested	(39,167)		15.06
Forfeited	(193,667)	$	11.87
Unvested balance at December 31, 2022	1,229,166	$	2.98

As of December 31, 2022, the total unrecognized expense related to all RSUs was $2.8 million, which the Company expects to recognize over a weighted-average period of 1.8 years.

Employee Stock Purchase Plan

The Company's 2020 Employee Stock Purchase Plan, or the ESPP, became effective on February 28, 2020. The ESPP authorizes the issuance of up to 1,435,619 shares of the Company's common stock. Of this amount, 1,119,914 were available for future grants as of December 31, 2022. The number of shares of the Company's common stock that may be issued pursuant to rights granted under the ESPP shall automatically increase on January 1st of each year and continuing for ten years, in an amount equal to one percent of the total number of shares of the Company's common stock outstanding on December 31st of the preceding calendar year, subject to the discretion of the board of directors or compensation committee to determine a lesser number of shares shall be added for such year. As a result, on January 1, 2023, the number of shares reserved for issuance under the ESPP increased by 546,147 shares, resulting in a total of 1,981,766 shares authorized for issuance.

Under the ESPP, eligible employees can purchase the Company's common stock through accumulated payroll deductions at such times as are established by the compensation committee. Eligible employees may purchase the Company's common stock at 85% of the lower of the fair market value of the Company's common stock on the first day of the offering period or on the last day of the offering period. The offering periods under the ESPP have a duration of

six months, with periods ending in May and November of each calendar year. Eligible employees may contribute up to 15% of their eligible compensation. Under the ESPP, a participant may not accrue rights to purchase more than $25,000 worth of the Company's common stock for each calendar year in which such right is outstanding or purchase more than 4,000 shares of the Company's common stock in any single offering period.

In accordance with the guidance in ASC 718-50, *Compensation – Stock Compensation*, the ability to purchase shares of the Company's common stock at 85% of the lower of the price on the first day of the offering period or the last day of the offering period (i.e. the purchase date) represents an option and**,** therefore, the ESPP is a compensatory plan under this guidance. Accordingly, share-based compensation expense is determined based on the option's grant-date fair value as estimated by applying the Black Scholes option-pricing model and is recognized over the withholding period. The Company recognized share-based compensation expense of $0.2 million and $0.4 million during the years ended December 31, 2022 and 2021, respectively, related to the ESPP.

13. Income Taxes

The tax effects of temporary differences that gave rise to significant portions of the deferred tax assets and liabilities were as follows:

	December 31,	
(in thousands)	**2022**	**2021**
Deferred tax assets:		
Net operating loss carryforwards	$ 64,547	$ 42,351
Research and development credits	32,068	22,244
Collaboration and license agreement	4,504	3,976
Capitalized research and development	65,012	51,806
Share-based compensation	11,312	11,245
Accrued expenses and other	1,922	4,654
Operating lease liabilities	8,900	-
Total gross deferred tax assets before valuation allowance	188,265	136,276
Valuation allowance	(179,843)	(135,053)
Net deferred tax assets	8,422	1,223
Deferred tax liabilities:		
Right of use assets - operating leases *(deferred rent for December 31, 2021)*	(7,609)	(876)
Depreciation	(813)	(347)
Total deferred tax liabilities	(8,422)	(1,223)
Net deferred taxes	$ -	$ -

In assessing the need for a valuation allowance, management must determine that there will be sufficient taxable income to allow for the realization of deferred tax assets. Based upon the historical and anticipated future losses, management has determined that the deferred tax assets do not meet the more-likely-than-not threshold for realizability. Accordingly, a full valuation allowance has been recorded against the Company's net deferred tax assets as of December 31, 2022 and 2021. The valuation allowance increased by $44.8 million and $72.1 million during the years ended December 31, 2022 and 2021, respectively.

A reconciliation of the federal income tax rate to the Company's effective tax rate is as follows:

	Year ended December 31,	
	2022	2021
Federal tax benefit at statutory rate	21.0 %	21.0 %
State tax, net of federal benefit	7.5	11.9
Permanent differences	(2.5)	(1.1)
Research and development and orphan tax credits	6.9	7.1
Change in valuation allowance	(32.9)	(38.9)
	- %	- %

The following table summarizes carryforwards of federal, state and local net operating losses, or NOL, and research and development and orphan drug tax credits:

	December 31,	
(in thousands)	2022	2021
Federal	$ 199,233	$ 126,551
State	199,230	126,547
Local	180,859	116,301
Research tax credits	32,068	22,244

For federal income tax purposes, $0.3 million of NOL carryforwards expire in 2037. The remaining federal NOL carryforwards were generated subsequent to January 1, 2018, and therefore, are able to be carried forward indefinitely.

For state income tax purposes, NOL carryforwards begin expiring in 2037, and expire through 2042.

For local income tax purposes related to the city of Philadelphia, NOL carryforwards begin expiring in 2023, and expire through 2042. NOL carryforwards generated prior to 2023 expire after 3 years, whereas NOL carryforwards generated in 2023 expire after 20 years.

As of December 31, 2022, the Company also had federal research and development and orphan drug tax credit carryforwards of $32.1 million that will begin to expire in 2038, unless previously utilized.

The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. NOL and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50 percent, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has not done an analysis to determine whether or not ownership changes have occurred since inception. Certain state NOL carryforwards may also be limited, including Pennsylvania, which limits NOL utilization as a percentage of apportioned taxable income.

The Company will recognize interest and penalties related to uncertain tax positions as a component of interest income, net. As of December 31, 2022, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statement of operations. Tax years from 2019 and after remain subject to examination by the taxing jurisdictions. The NOL and tax credit carryforwards remain subject to review until utilized.

14. Subsequent Events

None.

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

None.

Item 9A. *Controls and Procedures*

Conclusions Regarding the Effectiveness of Disclosure Controls and Procedures

Under the supervision of and with the participation of our management, including our chief executive officer, who is our principal executive officer, and our chief financial officer, who is our principal financial officer, we conducted an evaluation of the effectiveness of our disclosure controls and procedures as of December 31, 2022, the end of the period covered by this Annual Report. The term "disclosure controls and procedures," as set forth 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 provide reasonable assurance that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the rules and forms promulgated by the SEC. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, 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 management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2022, our chief executive officer and chief financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

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 chief executive officer and chief financial officer and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

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

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Additionally, in designing disclosure controls and procedures, our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible disclosure controls and procedures. The design of any disclosure controls and procedures also is based in part upon certain assumptions

about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions.

Our management, with the participation of our chief executive officer and chief 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 *Internal Control – Integrated Framework (2013)*. 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 independent registered public accounting firm regarding internal control over financial reporting. For as long as we remain an "emerging growth company" as defined in Section 2(a) of the Securities Act of 1933, or the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, we intend to take advantage of the exemption permitting us not to comply with the requirement that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2022, that have materially affected, or are reasonably likely to materially affect, our internal controls 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 to 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 to 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 to 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 to 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 to 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***

(1) *Financial Statements:*

The financial statements required by Item 15(a) are filed as part of this Annual Report on Form 10-K under Item 8 "Financial Statements and Supplementary Data."

(2) *Financial Statement Schedules*

The financial statement schedules required by Item 15(a) are omitted because they are not applicable, not required or the required information is included in the financial statements or notes thereto as filed in Item 8 of this Annual Report on Form 10-K.

(3) *Exhibits.*

Exhibit Number	Description	Form	File No.	Exhibit Filing Date	Filed/ Furnished Herewith
3.1	Restated Certificate of Incorporation, dated March 3, 2020.	10-Q	001-39231	May 11, 2020	
3.2	Amended and Restated Bylaws, dated December 1, 2022.	8-K	001-39231	December 2, 2022	
4.1	Form of Common Stock Certificate	S-1/A	333-236214	February 18, 2020	
4.2	Amended and Restated Investors' Rights Agreement, dated August 21, 2019, by and among the Registrant and certain of its stockholders.	S-1	333-236214	February 3, 2020	
4.3	Description of Registrant's Securities	10-K	001-39231	March 3, 2021	
10.1†^	Development Services and Clinical Supply Agreement, dated April 13, 2020, by and between the Registrant and Catalent Maryland, Inc.	10-Q	001-39231	May 11, 2020	
10.2	Lease, dated April 10, 2020, by and between the Registrant and Commerce Square Partners - Philadelphia Plaza, L.P.	10-Q	001-39231	May 11, 2020	
10.3	First Amendment to Lease, dated April 10, 2020, by and between the Registrant and Philadelphia Plaza – Phase II LP	10-Q	001-39231	May 11, 2020	
10.4	Form of Indemnification Agreement between the Registrant and its directors and officers	S-1	333-236214	February 3, 2020	

10.5	Amended and Restated 2018 Equity Incentive Plan, as amended, and forms of award agreements.	S-1	333-236214	February 3, 2020
10.6	2020 Equity Incentive Plan of the Registrant, and forms of award agreements.	S-1/A	333-236214	February 18, 2020
10.7	2020 Employee Stock Purchase Plan of the registrant	S-1/A	333-236214	February 18, 2020
10.8	Amended and Restated Employment Agreement dated February 14, 2020, by and between the Registrant and Bruce Goldsmith.	S-1/A	333-236214	February 18, 2020
10.9	Consulting Agreement, dated January 8, 2019, as amended on January 31, 2020, by and between the Registrant and James Wilson, M.D., Ph.D.	S-1	333-236214	February 3, 2020
10.10†^	Amended and Restated Sponsored Research, Collaboration and License Agreement, dated May 5, 2020, by and between the Registrant and The Trustees of the University of Pennsylvania.	10-Q	001-39231	August 13, 2020
10.11^	Amendment No. 1, dated August 13, 2020, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	10-Q	001-39231	November 10, 2020
10.12^	Amendment No. 2, dated November 2, 2020, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	S-1	333-252213	January 19, 2021
10.13†^	Amendment No. 3, dated December 9, 2020, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	S-1	333-252213	January 19, 2021
10.14^	Lease, dated December 15, 2020 by and between the Registrant and Hopewell Campus Owner, LLC	8-K	001-39231	December 18, 2020
10.15	2021 Equity Inducement Plan	S-8	333-258000	July 19, 2021

10.16†^	Amendment No. 4, dated June 2, 2021, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	10-K	001-39231	March 3, 2022	
10.17	Amendment No. 5, dated August 3, 2021, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	10-Q	001-39231	November 4, 2021	
10.18†^	Amendment No. 6, dated November 12, 2021, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	10-K	001-39231	March 3, 2022	
10.19†^	Amendment No. 7, dated December 3, 2021, to the Amended and Restated Sponsored Research, Collaboration and License Agreement by and between the Registrant and the Trustees of the University of Pennsylvania	10-K	001-39231	March 3, 2022	
10.20†^	Eighth Amendment to Amended and Restated Research, License & Collaboration Agreement, dated May 11, 2022, by and between the Registrant and the Trustees of the University of Pennsylvania.	10-Q	001-39231	August 4, 2022	
10.21+	Employment Agreement, dated August 23, 2021 by and between the Registrant and Simona King.	10-Q	001-39231	November 4, 2021	
10.22+†	Employment Agreement, dated October 10, 2022 by and between the Registrant and William Chou.	10-Q	001-39231	November 10, 2022	
10.23+†	Transition and Separation Agreement, dated May 27, 2022 by and between the Registrant and Bruce Goldsmith.	10-Q	001-39231	August 4, 2022	
10.24+†	Employment Agreement dated September 10, 2019, as amended on February 26th, 2020, by and between the Registrant and Edgar B. (Chip) Cale.				X

10.25+†	Employment Agreement, dated July 22, 2019, as amended on February 14, 2022, by and between the Registrant and Alexandros Fotopoulos.	S-1/A	333-236214	February 18, 2020	
10.26+†	Transition and Separation Agreement, dated November 17, 2022, by and between the Registrant and Monika Toernsen.				X
23.1	Consent of KPMG LLP, an independent registered public accounting firm.				X
24.1	Power of Attorney. Reference is made to the signature page hereto.				X
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				X
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				X
32.1*	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
32.2*	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
101.INS	Inline XBRL Instance Document				X
101.SCH	XBRL Taxonomy Extension Schema Document				X
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.				X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.				X
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.				X

101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.	X
104	Cover Page Interactive Data File (formatted as Inline XBRL).	X

+ Indicates management contract or compensatory plan, contract or agreement.

† Registrant has omitted portions of the exhibit as permitted under Item 601(b)(10) of Regulations S-K.

^ Registrant has omitted schedules and exhibits pursuant to Item 601(a)(5) of Regulation S-K. The Registrant agrees to furnish supplementally a copy of the omitted schedules and exhibits to the SEC upon request.

* This certification is deemed not filed for purposes of section 18 of the Exchange Act or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act.

Item 16. Form 10-K Summary.

Registrants may voluntarily include a summary of information required by Form 10-K under Item 16. We have elected not to include such summary.

SIGNATURES

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

PASSAGE BIO, INC.

Date: March 6, 2023

By: /s/ William Chou, M.D.
Name: William Chou, M.D.
Title: Chief Executive Officer and Director

Date: March 6, 2023

By: /s/ Simona King
Name: Simona King
Title: Chief Financial Officer

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints William Chou, M.D., Simona King and Edgar B. Cale, and each of them, with full power of substitution and resubstitution, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this Annual Report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agents full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorney-in-fact and agents or his substitute or substitutes may lawfully do or cause to be done by virtue thereof. 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/ William Chou, M.D. William Chou, M.D.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 6, 2023
/s/ Simona King Simona King	Chief Financial Officer and Corporate Secretary *(Principal Financial and Accounting Officer)*	March 6, 2023
/s/ Maxine Gowen, Ph.D. Maxine Gowen, Ph.D.	Director	March 6, 2023
/s/ Athena Countouriotis, M.D. Athena Countouriotis, M.D.	Director	March 6, 2023
/s/ Saqib Islam Saqib Islam	Director	March 6, 2023
/s/ Sandip Kapadia Sandip Kapadia	Director	March 6, 2023
/s/ Michael Kamarck, Ph.D. Michael Kamarck, Ph.D.	Director	March 6, 2023
/s/ Derrell Porter, M.D. Derrell Porter, M.D.	Director	March 6, 2023
/s/ Tom Woiwode, Ph.D. Tom Woiwode, Ph.D.	Director	March 6, 2023

About Passage Bio

Passage Bio (Nasdaq: PASG) is a clinical stage genetic medicines company on a mission to provide life-transforming therapies for patients with CNS diseases with limited or no approved treatment options. Our portfolio spans pediatric and adult CNS indications, and we are currently advancing clinical programs in GM1 gangliosidosis and frontotemporal dementia and our preclinical pipeline, including programs in amyotrophic lateral sclerosis and Huntington's disease. Based in Philadelphia, PA, our company has established a strategic collaboration and licensing agreement with the renowned University of Pennsylvania's Gene Therapy Program to conduct our discovery and IND-enabling preclinical work. Through this collaboration, we have enhanced access to a broad portfolio of gene therapy candidates and future gene therapy innovations that we then pair with our deep clinical, regulatory, manufacturing and commercial expertise to rapidly advance our robust pipeline of optimized gene therapies. As we work with speed and tenacity, we are always mindful of patients who may be able to benefit from our therapies.

Leadership Team

William Chou, M.D., Chief Executive Officer

Edgar B. (Chip) Cale, General Counsel & Corporate Secretary

Mark Forman, M.D., Ph.D., Chief Medical Officer

Alex Fotopoulos, Chief Technical Officer

Stuart Henderson, Senior Vice President, Corporate Development & Investor Relations

Simona King, Chief Financial Officer

Desiree Luthman, Senior Vice President, Global Regulatory Affairs

James M. Wilson, M.D., Ph.D., Chief Scientific Advisor

Board of Directors

William Chou, M.D.

Athena Countouriotis, M.D.

Maxine Gowen, Ph.D., Chairwoman

Saqib Islam

Michael Kamarck, Ph.D.

Sandip Kapadia

Derrell D. Porter, M.D.

Thomas Woiwode, Ph.D.

Corporate Counsel

Fenwick & West LLP
San Francisco, CA

Independent Auditors

KPMG LLP
1601 Market Street
Philadelphia, PA 19103-2499

Transfer Agent & Registrar

Computershare Trust Company, N.A.
Shareholder Services
(800) 736-3001 or (781) 575-3100
P.O. Box 43078
Providence, RI 02940-3078

Common Stock

Passage Bio, Inc., common stock is traded on the Nasdaq Global Select Market under the ticker PASG.

Annual Meeting (Virtual)

Thursday, May 25, 2023, 10:00 am ET

Forward-Looking Statements

This annual report contains "forward-looking statements" within the meaning of, and made pursuant to the safe harbor provisions of, the Private Securities Litigation Reform Act of 1995, including, but not limited to: our expectations about timing and execution of anticipated milestones, including progress of clinical trials and the availability of clinical data from such trials; our expectations about our collaborators' and partners' ability to execute key initiatives; our expectations about manufacturing plans and strategies; our expectations about cash runway; and the ability of our lead product candidates to treat their respective target monogenic CNS disorders. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "might," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our ability to develop and obtain regulatory approval for our product candidates; the timing and results of preclinical studies and clinical trials; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events; the risk that positive results in a preclinical study or clinical trial may not be replicated in subsequent trials or success in early stage clinical trials may not be predictive of results in later stage clinical trials; failure to protect and enforce our intellectual property, and other proprietary rights; our dependence on collaborators and other third parties for the development and manufacture of product candidates and other aspects of our business, which are outside of our full control; risks associated with current and potential delays, work stoppages, or supply chain disruptions; and the other risks and uncertainties that are described in the Risk Factors section in documents the company files from time to time with the Securities and Exchange Commission (SEC), and other reports as filed with the SEC. Passage Bio undertakes no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

Passage Bio
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