2022 Annual Report

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: 001-40030

DECIBEL THERAPEUTICS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware	**46-4198709**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
1325 Boylston Street, Suite 500 Boston, Massachusetts	**02215**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 370-8701

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, par value $0.001 per share	DBTX	The Nasdaq Stock Market LLC

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 15(d) of the Act. YES ☐ NO ☒

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 ☒

As of June 30, 2022, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was $70.8 million based upon the closing sale price of the registrant's common stock on that date.

The number of shares of registrant's Common Stock outstanding as of March 1, 2023 was 25,014,984.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A relating to the 2023 Annual Meeting of Stockholders within 120 days of the end of the registrant's fiscal year ended December 31, 2022. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

Table of Contents

Cautionary Note Regarding Forward-Looking Statements and Industry Data

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue" "could," "estimate," "expect," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "target," "would," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the initiation, timing, progress and results of our current research and development programs, preclinical studies and clinical trials;
- our estimates regarding expenses, future revenue, capital requirements and need for additional financing;
- our plans to develop our product candidates and programs;
- the timing of and our ability to submit applications for, obtain and maintain regulatory approvals for our product candidates;
- our estimates regarding the potential patient populations for our product candidates and programs;
- our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash, cash equivalents and available-for-sale securities;
- the potential advantages of our product candidates and programs;
- the potential advantages of our platform;
- the rate and degree of market acceptance and clinical utility of our product candidates and programs;
- our estimates regarding the potential market opportunity for our product candidates and programs;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates;
- the impact of government laws and regulations;
- our competitive position;
- developments relating to our competitors and our industry;
- our ability to maintain and establish collaborations or obtain additional funding;
- the potential direct or indirect impact of the COVID-19 pandemic on our business; and
- our expectations regarding the time during which we will be an emerging growth company under the Jumpstart our Business Startup Acts of 2012.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the "Risk Factor Summary" below and in Part I, Item 1A "Risk Factors," that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we reference herein and have filed or incorporated by reference hereto completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report on Form 10-K are made as

of the date of this Annual Report on Form 10-K, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. The market data used in this Annual Report on Form 10-K involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Although we are responsible for the disclosure contained in this Annual Report on Form 10-K and we believe the information from industry publications and other third-party sources included in this Annual Report on Form 10-K is reliable, such information is inherently imprecise. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

Risk Factor Summary

Our business is subject to a number of risks of which you should be aware before making an investment decision. Below we summarize what we believe to be the principal risks facing our business, in addition to the risks described more fully in Part I, Item 1A, "Risk Factors" of this Annual Report on Form 10-K and other information included in this report. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations.

If any of the following risks occurs, our business, financial condition and results of operations and future growth prospects could be materially and adversely affected, and the actual outcomes of matters as to which forward-looking statements are made in this report could be materially different from those anticipated in such forward-looking statements.

- We have incurred significant losses since our inception, have no products approved for sale and we expect to incur substantial losses for the foreseeable future and may never achieve or maintain profitability;
- We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our research and development programs or commercialization efforts;
- The report of our independent registered public accounting firm included a "going concern" explanatory paragraph;
- The COVID-19 pandemic disrupted our ongoing Phase 1b clinical trial of DB-020 and has affected and may in the future affect our ability to initiate and complete preclinical studies, delay the initiation of our planned clinical trials or future clinical trials, disrupt regulatory activities, disrupt our manufacturing and supply chain or have other adverse effects on our business and operations. In addition, this pandemic has caused substantial disruption to global supply chains and may adversely impact economies worldwide, both of which could result in adverse effects on our business, operations and ability to raise capital;
- Our limited operating history may make it difficult for stockholders to evaluate the success of our business to date and to assess our future viability;
- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel;
- We are early in our development efforts. Our business is dependent on our ability to advance our lead gene therapy product candidate, DB-OTO, and our other current and future product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them. If we are unable to complete preclinical and clinical development, obtain regulatory approval for or commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed;
- Clinical development involves a lengthy and expensive process with uncertain outcomes, and results of earlier studies and trials may not be predictive of future clinical trial results. If our preclinical studies and clinical trials are not sufficient to support regulatory approval of any of our product candidates, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development of such product candidate;
- Gene therapy is an emerging field of drug development that poses many risks. We have only limited prior experience in gene therapy research and no prior experience in gene therapy clinical development. Our lack of experience and the limited patient populations for our gene therapy programs may limit our ability to be successful or may delay our development efforts;
- If we experience delays or difficulties in participant enrollment for clinical trials, our research and development efforts and the receipt of necessary regulatory approvals could be significantly delayed or prevented;
- Our product candidates or the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval;
- The manufacture of gene therapy products is complex and difficult and is subject to a number of scientific and technical risks, some of which are common to the manufacture of drugs and biologics and others of which are unique to the manufacture of gene therapies. We could experience manufacturing problems that result in delays in our gene therapy development or commercialization programs;

- We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, research, preclinical and clinical testing, and these third parties may not perform satisfactorily;
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do;
- Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could harm our business; and
- Our rights to develop and commercialize any product candidates are subject and may in the future be subject, in part, to the terms and conditions of licenses granted to us by third parties. If we fail to comply with our obligations under our current or future intellectual property license agreements, including applicable diligence milestones, or otherwise experience disruptions to our business relationships with our current or any future licensors, we could lose intellectual property rights that are important to our business.

PART I

Item 1. Business.

Overview

We are a clinical-stage biotechnology company dedicated to discovering and developing transformative treatments for hearing and balance disorders, one of the largest areas of unmet need in medicine. We aim to restore and improve hearing and balance through the restoration and regeneration of functional hair cells and non-sensory support cells within the inner ear. We have built a proprietary platform that integrates single-cell genomics and bioinformatics analyses, precision gene therapy technologies and our expertise in inner ear biology. We are leveraging our platform to advance our pipeline of clinical and preclinical gene therapy programs that are designed to selectively replace genes for the treatment of congenital, monogenic hearing loss and to regenerate inner ear hair cells for the treatment of acquired hearing and balance disorders. We are developing our lead gene therapy product candidate, DB-OTO, to provide durable, high quality, physiological hearing to individuals with profound, congenital hearing loss caused by mutations of the otoferlin, or OTOF, gene. In addition to DB-OTO, we are advancing AAV.103 to restore hearing in individuals with mutations in the gap junction beta-2, or GJB2, gene, AAV.104 to restore hearing in individuals with mutations in the stereocilin, or STRC, gene and AAV.105 to restore hearing in individuals with another single gene mutation. We also have gene therapy programs to convert supporting cells, the cells adjacent to hair cells, into either cochlear or vestibular hair cells in order to restore hearing or balance function. In addition to our gene therapy programs, we are developing DB-020 for the prevention of cisplatin-induced hearing loss. We ceased enrolling patients in our Phase 1b clinical trial of DB-020, subsequent to announcing the positive results from the interim analysis from the first 19 patients enrolled in the trial.

We are focused on both hearing loss and balance disorders due to their widespread impact and shared biology. Hearing loss is one of the largest areas of unmet need in medicine and affects approximately 466 million people worldwide, including 48 million people in the United States. Hearing loss can significantly impact mental health, cognition and language development. Beyond hearing loss, dysfunction of the inner ear can lead to severe impairments in balance. Approximately eight million people in the United States report chronic balance problems, which can lead to significant life impairment and an increased risk of falls, potentially resulting in hospitalization, limited mobility and depression. Despite these impacts, there are no approved therapies for the treatment of hearing loss or balance disorders.

We believe the lack of approved therapies is caused in part by the complex biology of the inner ear, and we have built our platform to overcome this challenge. We are applying proprietary analyses of gene expression in the cochlea, the organ within the inner ear responsible for hearing, and the vestibule, the set of organs within the inner ear responsible for balance, to generate a comprehensive database of expression profiles in every known inner ear cell type. Our database currently includes over three million cellular gene expression profiles from several mammalian species, which we believe is the largest dataset of its kind for the inner ear. We are using this dataset to identify and select targets, including reprogramming factors to promote inner ear hair cell regeneration, and cell-selective promoters to drive precise expression of transgenes in therapeutically relevant cell types of the inner ear. Combining our extensive understanding of the molecular profile of the inner ear with recent learnings and successes in genetic medicine, we are using adeno-associated virus, or AAV, vectors to deliver potentially restorative gene therapies that are designed to selectively express transgenes only in targeted cell types important to hearing and balance. We believe AAV gene therapy is an ideal modality for inner ear disorders because the inner ear is a small, enclosed compartment that provides the opportunity for local delivery of high vector concentrations, which may increase transgene expression in the target cell type, limit systemic exposure to improve safety and reduce the volume of AAV needed. We have observed that hair cells and other non-sensory support cell types are readily transduced by multiple natural AAV serotypes in non-human primates. Additionally, inner ear hair cells are non-dividing, which means that AAV vector genomes are not diluted, eliminating a hurdle for achieving durable expression following a single administration of AAV gene therapy.

We are developing our lead gene therapy product candidate, DB-OTO, which is designed to be a one-time AAV-based gene therapy, to provide durable, high quality, physiological hearing to individuals with profound, congenital hearing loss caused by mutations of the OTOF gene. OTOF is a protein expressed in the inner hair cells of the cochlea that enables communication between sensory cells of the inner ear and the auditory nerve by regulating synaptic transmission. We estimate approximately 20,000 individuals in the United States and the major markets in Europe suffer from hearing loss caused by mutations of the OTOF gene. At present, the only treatment option for these individuals is a cochlear implant, or CI. However, while CIs provide a clear benefit over profound hearing loss, CIs are assistive devices and have significant limitations.

We have designed DB-OTO utilizing a proprietary, cell-selective promoter to provide expression of OTOF that is limited to hair cells. In our preclinical studies, the hair cell-selective expression of OTOF provided by DB-OTO enabled restoration of hearing in mice that was more durable than when OTOF was expressed under the control of a ubiquitous

promoter, which is designed to drive expression in all cells. In addition to the loss of durability, we observed that use of a ubiquitous promoter in mice resulted in the loss of inner hair cells throughout the cochlea. DB-OTO is designed to be delivered locally to patients using the surgical approach employed by neurotologists and pediatric otolaryngologists during a standard cochlear implantation procedure. We believe the cell-selective expression of DB-OTO and its delivery by this established surgical procedure will provide a core competitive advantage important to the success of DB-OTO.

In October 2022, we received clearance from the U.S. Food and Drug Administration, or the FDA, for our Investigational New Drug, or IND, application to initiate CHORD™, a Phase 1/2 dose escalation clinical trial of DB-OTO in pediatric patients, and in January 2023 we received approval from the United Kingdom, or the U.K., Medicines and Healthcare Products Regulatory Agency, or MHRA, for our Clinical Trial Application, or CTA, for the trial. The Phase 1/2 clinical trial is designed to evaluate the safety, tolerability and efficacy of DB-OTO in pediatric patients with congenital hearing loss caused by mutations of the OTOF gene. In addition to safety and tolerability endpoints, established, clinically relevant, objective and behavioral measurements of hearing will be used as efficacy endpoints in the clinical trial. The auditory brainstem response, or ABR, will serve as an early, objective, clinically accepted readout of hearing thresholds in the clinical trial. ABR is a physiologic measure of hearing sensitivity routinely used in diagnosis of newborn hearing loss. Individuals with OTOF-related hearing loss typically have no detectable ABR. We have previously used ABR to characterize dose-response of DB-OTO after intra-cochlear delivery in translational animal studies. We expect the first two participants in the U.S. portion of the Phase 1/2 clinical trial will be as young as seven years of age and that subsequent participants will include children as young as two years of age and infants younger than two years of age. We expect to dose infants two years of age and younger in the U.K. portion of the Phase 1/2 clinical trial. We have commenced trial site startup activities and expect to initiate the Phase 1/2 clinical trial of DB-OTO in the first half of 2023. We anticipate reporting the initial safety and tolerability data and preliminary efficacy data, as measured by ABR, from the first patients in the Phase 1/2 clinical trial in the first quarter of 2024. The FDA has granted orphan drug designation and rare pediatric disease designation for DB-OTO for the treatment of OTOF-related, congenital hearing loss.

In addition to DB-OTO, we are advancing AAV.103, AAV.104 and AAV.105, gene therapy programs targeting hearing loss resulting from other single gene mutations, or monogenic, forms of hearing loss. AAV.103 aims to restore hearing in individuals with mutations in the GJB2 gene, AAV.104 aims to restore hearing in individuals with mutations in the STRC gene and AAV.105 aims to restore hearing in individuals with another single gene mutation. We have identified a product candidate for our AAV.103 program. We are continuing to conduct preclinical efficacy experiments, which we expect to inform the potential clinical development plan for our AAV.103 program.

We are also using our platform to design and develop a pipeline of gene therapies for hair cell regeneration within the inner ear. We are engineering gene therapies to convert supporting cells, the cells adjacent to hair cells, into either cochlear or vestibular hair cells in order to restore hearing or balance function. These gene therapy programs are designed to express the developmental or reprogramming factors that regulate cell fate and use our proprietary, cell-selective promoters to control expression spatially and temporally. Our vestibular hair cell regeneration program, which includes DB-ATO and AAV.201, is designed to restore balance by promoting regeneration of hair cells in the vestibular system, the sensory system responsible for balance. In this program, we are focused on the development of a treatment for bilateral vestibulopathy, or BVP, a debilitating, acquired condition that significantly impairs balance, mobility and stability of vision. Many BVP patients lack vestibular hair cells yet retain vestibular supporting cells. We estimate there are approximately 130,000 adults in the United States and the major markets in Europe with BVP. There are no approved therapies for BVP and the current standard of care, which is focused on rehabilitation and lifestyle changes, does not address the underlying loss of vestibular hair cells often responsible for the condition. In addition, we are advancing our cochlear hair cell regeneration program to treat acquired hearing loss by regenerating cochlear outer hair cells.

In addition to our gene therapy product candidates and programs, we are developing a clinical-stage product candidate, DB-020, for the prevention of cisplatin-induced hearing loss. DB-020 is a novel formulation of sodium thiosulfate, or STS, that we have optimized for local delivery to the ear. STS inactivates cisplatin, a widely used chemotherapy that often leads to hearing loss and related complications in patients being treated for cancer. We are developing DB-020 to prevent cisplatin-induced hearing loss without impacting the beneficial, anti-tumor effect of cisplatin. In 2019, we completed a randomized, double-blind, placebo-controlled Phase 1 clinical trial of DB-020 in healthy volunteers, in which DB-020 was well tolerated. Following the Phase 1 clinical trial, we initiated a randomized, double-blind, placebo-controlled, multicenter Phase 1b clinical trial in 2020 to evaluate the safety and efficacy of DB-020 for the prevention of cisplatin-induced hearing loss. In June 2022, we reported positive topline data from an interim analysis of the ongoing Phase 1b clinical trial.

We ceased enrollment of patients in our Phase 1b clinical trial of DB-020, subsequent to the positive results from the interim analysis from the first 19 patients enrolled. We plan to report additional data from the interim analysis in 2023, and we are working with key opinion leaders to integrate learnings from the interim analysis into an updated clinical development plan. We expect to consult with regulatory agencies in 2023 as part of that planning. We are considering a range of potential

approaches by which to advance DB-020, including entering into strategic collaborations with third parties for the further development and commercialization of DB-020. The FDA has granted fast track designation for DB-020 for the prevention of cisplatin-related ototoxicity.

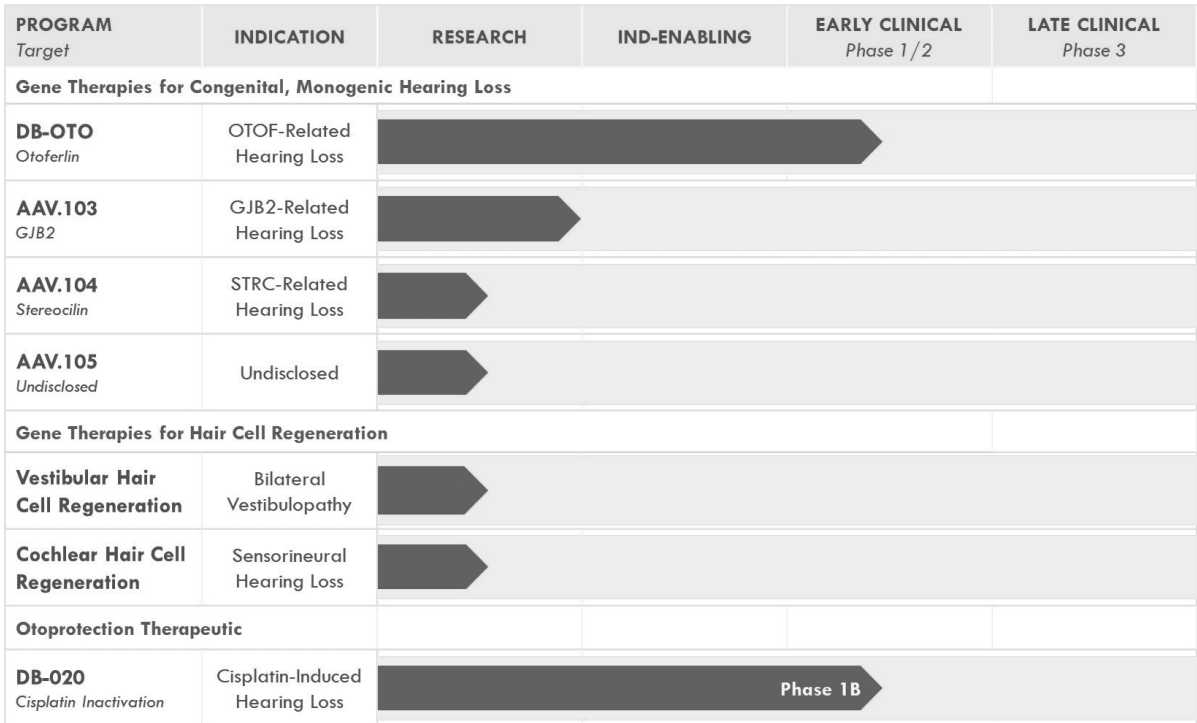
In 2017, we entered into a strategic collaboration with Regeneron Pharmaceuticals, Inc., or Regeneron, that is focused on developing gene therapies for monogenic forms of congenital hearing loss. Under the collaboration, we are developing DB-OTO, AAV.103 and AAV.104 with Regeneron using discovery teams from Regeneron and its mouse and human genetics research platforms and gene therapy capabilities. In addition to paying us upfront fees and a fee associated with extending the research term of the collaboration, Regeneron has agreed to pay milestones and reimburse costs on a product-by-product basis intended to reflect approximately half of the development costs. We retain worldwide development and commercialization rights to all products developed under the collaboration and have agreed to pay Regeneron tiered royalties on net sales of products developed under the collaboration. In October 2020, we amended the collaboration with Regeneron, and the ATOH1 target under our vestibular hair cell regeneration program was removed from the collaboration. Because ATOH1 was previously being developed with Regeneron under the collaboration, we agreed, as part of the amendment, to pay to Regeneron a royalty calculated as a low-to mid-single digit percentage of net sales of the product candidate, DB-ATO, designed to express ATOH1. In February 2023, we further amended the collaboration with Regeneron to provide for accelerated payments by Regeneron to us for clinical development milestones for DB-OTO and pre-IND milestones for AAV.103.

Our Pipeline

We have built a pipeline to further our vision of creating a world of connection for people with hearing and balance disorders. Our portfolio of product candidates and programs is primarily derived from our proprietary platform and is focused in three areas:

- **Gene Therapies for Congenital, Monogenic Hearing Loss** designed to restore functional cells within the cochlea to address hearing disorders caused by single gene mutations
- **Gene Therapies for Hair Cell Regeneration** designed to replace lost hair cells within the inner ear to address acquired hearing loss and balance disorders
- **Otoprotection Therapeutic** in clinical development to prevent hearing loss in cancer patients undergoing chemotherapy with cisplatin

We retain worldwide development and commercialization rights to all of our product candidates and programs.



Strategy

Our goal is to transform the lives of people with hearing and balance disorders. We intend to establish ourselves as the leading biotechnology company focused on hearing and balance disorders by discovering, developing and commercializing innovative gene therapies for restoration of function of hair cells and non-sensory support cells and regeneration of hair cells within the inner ear. We aim to accomplish this goal by implementing the following strategies:

- **Advance our lead gene therapy product candidate, DB-OTO, through clinical development and regulatory approval.** We are developing DB-OTO to provide hearing to individuals with profound, congenital hearing loss caused by mutations of the OTOF gene. In our preclinical studies, the hair cell-selective expression of OTOF provided by DB-OTO enabled restoration of hearing in mice that was more durable than when OTOF was expressed under the control of a ubiquitous promoter. We have received clearance from the FDA and the MHRA to initiate CHORD™, a Phase 1/2 dose escalation clinical trial of DB-OTO in pediatric patients. The Phase 1/2 clinical trial is designed to evaluate the safety, tolerability and efficacy of DB-OTO in pediatric patients with congenital hearing loss due to an OTOF deficiency. In addition to safety and tolerability endpoints, established, clinically relevant, objective and behavioral measurements of hearing will be used as efficacy endpoints in the clinical trial.
- **Apply our platform capabilities to broaden our pipeline and develop gene therapies for congenital, monogenic hearing loss.** We are utilizing our platform and the learnings from the development of DB-OTO to develop AAV.103 to restore hearing in individuals with mutations in the GJB2 gene, AAV.104 to restore hearing in individuals with mutations in the STRC gene and AAV.105 to restore hearing in individuals with another single gene mutation. Each of these product candidates and programs benefits from the application of our platform to control expression of the transgene selectively in cell types where the endogenous gene is naturally expressed.
- **Develop novel gene therapy product candidates for regeneration of vestibular and cochlear hair cells.** We are designing gene therapies to restore balance in patients with BVP by regenerating lost hair cells in the vestibule and to restore hearing in patients with acquired hearing loss by regenerating lost hair cells in the cochlea. We are evaluating whether a single AAV vector delivering ATOH1 or a combination of ATOH1 and reprogramming factors may promote functional recovery. We are also evaluating the ability of selected reprogramming factors to regenerate cochlear hair cells to enable the design of gene therapies to treat common and acquired forms of hearing loss.
- **Continue to expand our proprietary platform through integration of single-cell genomics and bioinformatics, precision gene therapy technologies and inner ear expertise.** We are pioneering the integration of single-cell genomics and bioinformatics and precision gene therapy for the inner ear. We have generated what we believe is the largest database of inner ear, single-cell gene expression profiles and have utilized this database to identify and select cell-selective promoters and our gene therapy program targets, including reprogramming factors. We intend to further expand our product engine capabilities to enhance the therapeutic reach and productivity of our drug discovery process.
- **Maximize the value of our pipeline and our platform by exploring strategic collaborations.** Given the potential of our platform, we may opportunistically enter into strategic collaborations around certain targets or programs. We may seek strategic collaborations where we believe the resources and expertise of a third-party pharmaceutical or biotechnology company could be beneficial to the development or commercialization of our product candidates, could advance our programs to maximize their market potential or could expand our platform capabilities, as our Regeneron collaboration has done. We believe that the benefits of a strategic collaboration could be valuable to us with respect to the further development and commercialization of DB-020.

Our Opportunity – Hearing Loss and Balance Disorders

Hearing Loss

Globally, the World Health Organization, or WHO, estimates that 466 million people, including 34 million children, have disabling hearing loss. There are approximately 48 million people living in the United States with hearing loss. Children with hearing loss often experience delays in language development despite the use of hearing aids or CIs. These children are also at increased risk of impairment in executive functioning, which manifests itself in concentration, problem solving and working memory deficits. In the elderly, the neurocognitive impacts of hearing loss are also profound. Hearing loss during middle age was identified as the highest relative risk for dementia amongst all modifiable and non-modifiable risks according to a recent Lancet Commission report. Across all ages, hearing loss profoundly limits an individual's connection to the

environment and to other people, resulting in limited social interactions, feelings of loneliness and isolation. The WHO estimates that the global cost of unaddressed hearing loss is approximately $750 billion due to health sector costs (excluding the cost of hearing devices), costs of educational support, loss of productivity and societal costs. Despite these significant costs, no therapies to restore hearing have been approved by the FDA or, to our knowledge, other international regulatory agencies.

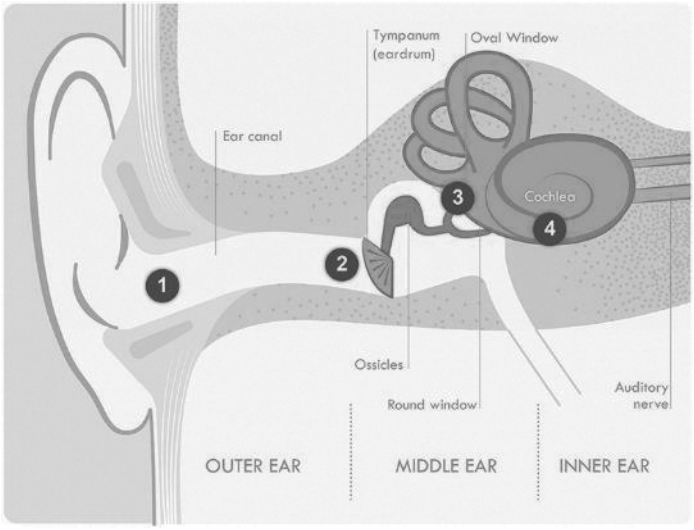
There are two primary categories of hearing loss: conductive, which occurs from physical interference of sound transmission in the ear canal or middle ear, and sensorineural, which occurs from dysfunction of the cochlea or auditory nerve in the inner ear. Hearing loss at birth is termed congenital hearing loss and affects approximately 1.7 out of every 1,000 children born in the United States. The majority of permanent, congenital hearing loss cases are sensorineural and result from a single gene defect. To date, over 90 distinct genes have been identified by researchers that lead to non-syndromic, which means accompanied by no other signs or symptoms, congenital hearing loss when mutated. In approximately 80% of these cases, the hearing loss is autosomal recessive, or only occurs when both copies of a gene are mutated. Mutation of the OTOF and GJB2 genes are two of the most common causes of autosomal recessive, non-syndromic, congenital hearing loss. Mutations in the genes STRC, SLC26A4, Myosin15A, Cadherin23, TMPRSS3 and TMC1 are all also associated with autosomal recessive, non-syndromic congenital hearing loss.

Acquired hearing loss, which impacts both adults and children, may originate from both a genetic and non-genetic etiology. Use of certain medicines such as cisplatin, exposure to loud sounds and aging can all result in damage to the inner ear and ultimately hearing loss. Since the regenerative capacity of the mammalian inner ear is limited, damage to hair cells of the inner ear is considered permanent, often accumulates over years and may only be addressed through regenerative approaches. We believe the number of people with disabling hearing loss will continue to increase as the WHO estimates that 1.1 billion people aged 12 to 35 years are at risk of hearing loss due to exposure to elevated noise levels in recreational settings.

Our Sense of Hearing

As shown in the image below, (1) sound waves enter our ear through the air and into the outer ear where they (2) cause the tympanum (eardrum) to vibrate. This causes a series of small bones (ossicles) in the middle ear to vibrate, which (3) transmit these vibrations through a small membrane called the oval window. These vibrations (4) cause displacements of structures within the cochlea that are sensed by hair cells and converted into signals that our brain perceives as sound.

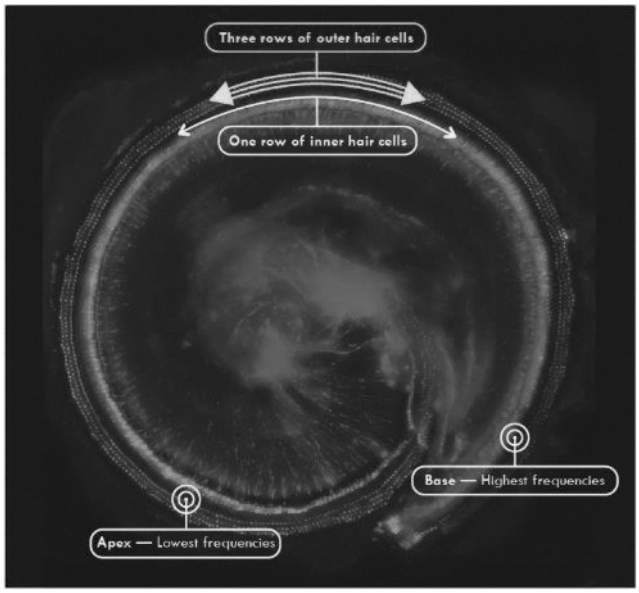
How Sound Waves Move from the Outer Ear to the Inner Ear



There are two types of sensory hair cells in the cochlea: outer hair cells and inner hair cells. Outer hair cells amplify quiet sounds, while inner hair cells primarily detect and transmit sound signals to the brain via the auditory nerve. There are approximately 15,000 hair cells in the human cochlea which are arranged in a tonotopic manner, meaning each region of the cochlea is activated by different sound frequencies. The image below is of a mouse cochlea and depicts three rows of outer hair cells, labeled in blue and indicated by the yellow arrows, and one row of inner hair cells, also labeled in blue, and

highlighted by the white arrows. The sound frequency map moves from the apex of the cochlea, which detects the lowest frequency sounds, to the base of the cochlea, which detects the highest frequency sounds.

Image of Outer Hair Cells and Inner Hair Cells in the Cochlea



Damage or dysfunction within these cells and cellular structures can lead to hearing loss, debilitating sensitivity to sound or tinnitus, which is a ringing in the ears. Importantly, once hair cells are lost for any reason, they do not naturally regenerate, and the resulting loss of function is permanent.

Diagnosis and Treatment of Hearing Loss

Every U.S. state has an established early hearing detection and intervention program and greater than 96% of newborns are screened within one month after birth. Newborns with severe-to-profound congenital hearing loss are routinely identified through this screening, which typically employs either ABR or otoacoustic emission, or OAE, which are non-invasive measures of inner ear hair cell function. ABR measures neural activity between inner hair cells and the brain in response to brief sounds, and OAEs measure whether outer hair cells in the cochlea appropriately respond to sound in the inner ear. Importantly, both ABR and OAE are similar across animal species and are routinely used to assess hearing in both human patients and preclinical animal models. A newborn that fails an initial screen will typically be given a full diagnostic assessment, including genetic testing in some cases, as a follow-up to confirm the finding and to potentially identify the underlying cause of the hearing loss.

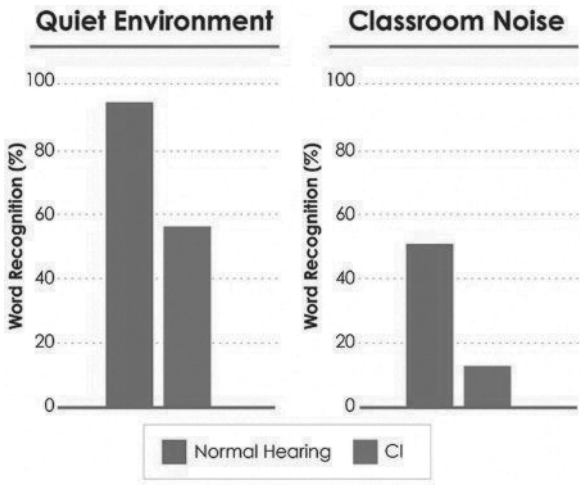
Adults that experience hearing loss may initially discuss this with their primary care physician but ultimately are likely to be tested by an audiologist and thereafter managed by an audiologist or otolaryngologist, trained as an ear, nose and throat specialist, or ENT. ENTs are the treating physicians for hearing loss and are trained as surgeons capable of performing cochlear implantation as well. In the United States, there are approximately 12,500 audiologists and 12,000 ENTs.

Current treatment options are severely limited for patients diagnosed with congenital or acquired hearing loss. Individuals with mild-to-moderate hearing loss, or a deficit of 25 to 55 decibels, or dB, from baseline, may be fitted with hearing aids. However, hearing aids are only able to amplify sounds too quiet to hear otherwise. Hearing aids are not able to address hearing loss due to disruptions in the hearing circuit.

Adults and children with severe-to-profound hearing loss, or deficits over 71 dB, are unable to perceive any speech. These individuals, who are not helped by hearing aids, may be candidates for cochlear implantation, which is the only approved treatment for hearing loss. CIs involve a surgically implanted electrode system that stimulates the auditory nerve, an external microphone, sound processor and transmitter system, which receive sounds from the environment. Only approximately 50% of children with severe-to-profound hearing loss in the United States receive a CI. Among adults who have developed severe-to-profound hearing loss in the United States, approximately 5% have chosen to have CIs. Historically, we estimate that the majority of individuals who have received a CI only received a CI in one ear.

CIs do not restore normal hearing and the surgical procedure potentially makes the implant incompatible with future restorative therapeutics of the cochlear hair cells for that ear. Although CIs have had a positive impact on many children with congenital hearing loss, they do not address the underlying pathophysiology and are only an assistive device for patients. The human inner ear has thousands of hair cells which provide a high-resolution signal to the brain to enable complex perception and human communication. CIs use between 8 and 24 electrodes to provide a signal to the brain, which results in a downsampling, or compression, of information and a severely degraded auditory signal. As a result, recipients of CIs often report difficulty understanding speech in real-world environments, even with low levels of background noise, and difficulty distinguishing complex components of sound like pitch and melody. Children with CIs are at risk of missing out on important social cues and information that influences their relationships. As shown in the image below, in an independent study of 46 children with normal hearing or CIs conducted by researchers at The Ohio State University, Columbus, the 27 children with CIs who were evaluated understood less than 20% of words in noise levels consistent with a classroom environment and less than 60% of words in a quiet environment when lip reading cues were not available.

Word Recognition with Normal Hearing vs. Cochlear Implants in Quiet Environment and Noise Levels Consistent with Classroom Settings



In addition, a recent third-party academic study has shown that approximately 50% of children with CIs were held back a grade during elementary school. Teenagers with CIs were also twice as likely as their peers to be enrolled in vocational training rather than tracking for university. Moreover, when the implant is taken off at night or for repair, the children are also once again disconnected from the auditory world. Finally, CIs can fail, resulting in revision surgeries or reimplantation in up to approximately 11% of cases.

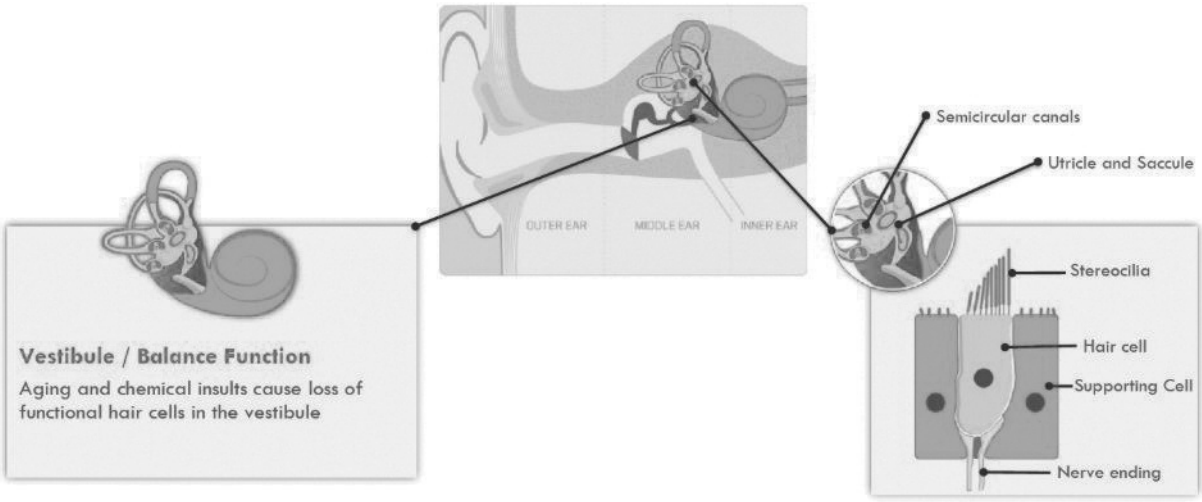
Balance Disorders

Beyond hearing loss, dysfunction of the inner ear may also result in severe impairments in balance due to damage in an individual's vestibular system. Loss of hair cells in the vestibular system can result from certain medicines or as a result of the aging process, which can lead to chronic balance problems and result in significant life impairment and an increased risk of falls. The National Institutes of Health, or NIH, estimates that up to eight million U.S. adults suffer from a chronic balance disorder. A subset of individuals with chronic balance disorders suffer from BVP, a profound bilateral loss of vestibular sensation. We estimate there are approximately 130,000 adults with BVP in the United States and the major markets in Europe.

Our Sense of Balance

The vestibular system, which is located in the inner ear as shown in the image below, provides information critical to our sense of balance. This system includes five sensory organs – three semicircular canal end organs and two otolith organs called the utricle and saccule – that work together to enable us to determine our position and movement in space. The vestibular system also helps to stabilize and coordinate vision and provide input to our musculoskeletal system by way of the brainstem and cerebellum, the brain's movement control center. Importantly, vestibular information is encoded by vestibular hair cells, which are evolutionarily linked to the hair cells within the cochlea.

The Vestibular System of the Inner Ear



Diagnosis and Treatment of Balance Disorders

Individuals who experience dizziness, vertigo or balance impairment are typically evaluated with objective, established tests to evaluate the function of the vestibular system. Many of these tests quantify the VOR. Additional objective measurements, including vestibular evoked myogenic potentials, or muscle activity in response to vestibular stimulation, are used to assess vestibular function. Many patients diagnosed with a vestibular disorder are prescribed rehabilitation or pharmacological interventions to manage the impact of symptoms. While there are treatments for the symptoms of vestibular disorders, there are no approved therapies that treat the underlying condition.

Our Platform

We have built a proprietary platform that integrates single-cell genomics and bioinformatics analyses, precision gene therapy technologies and our expertise in inner ear biology. We are leveraging our platform to advance gene therapy product candidates designed to selectively replace genes for congenital, monogenic hearing loss and to regenerate inner ear hair cells for acquired hearing and balance disorders.

Our platform consists of:

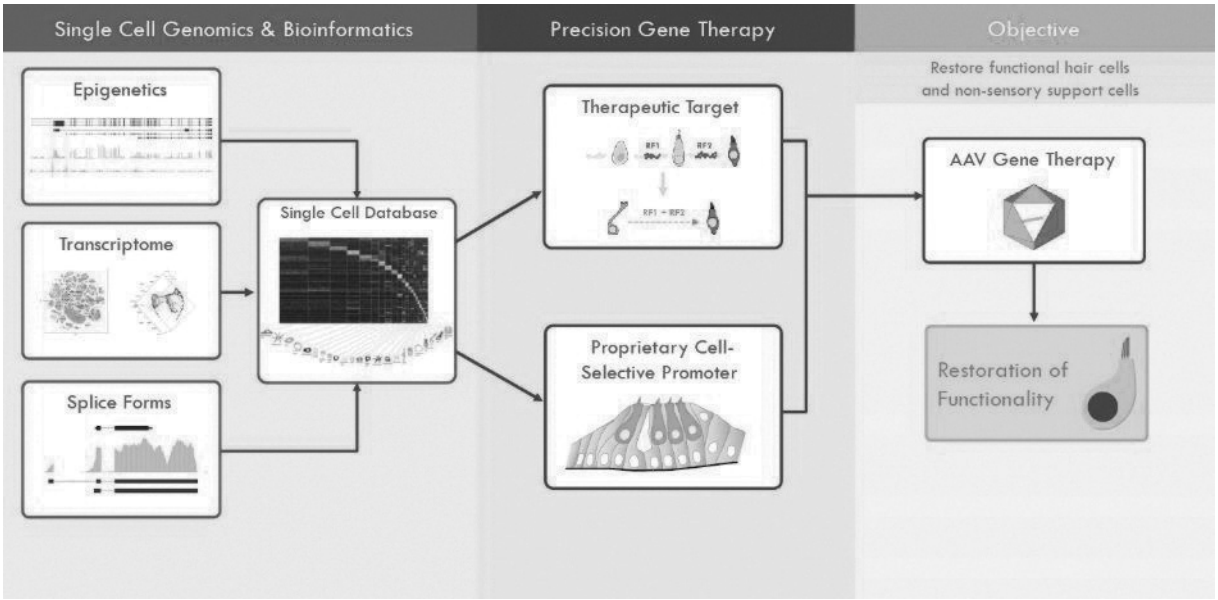
- **Single-Cell Genomics and Bioinformatics:** We are applying proprietary analyses of gene expression in the cochlea and vestibule and have generated a comprehensive database of every known inner ear cell type to enable target identification and evaluation, as well as identification and selection of promoters for gene therapies.
- **AAV Capsid Tropism Profiles for the Inner Ear:** We have built a comparative dataset of AAV capsid tropism in non-human primates to enable us to transduce therapeutically relevant cell types of the inner ear. Tropism means the ability of a virus to infect a particular cell.
- **Cell-Selective Promoter Library:** We have built a proprietary library of promoters to enable us to drive precise expression of transgenes in therapeutically relevant cell types.

Single-Cell Genomics and Bioinformatics

As depicted in the image below, we are optimizing and applying a series of single-cell genomics and bioinformatics approaches we believe to be essential for understanding the complex cellular diversity of the inner ear, including epigenetic capabilities to sequence regions of active DNA within cells, transcriptomic capabilities to characterize cell function and capabilities to enable identification of alternative transcript splicing.

We have applied these approaches to assemble a single-cell database of gene expression profiles from all known cell types within the inner ear. This comprehensive dataset includes over three million cellular transcriptional expression profiles from the cochlea and vestibule of several mammalian species. The proprietary dataset spans key stages of development from embryonic to adult and includes data we generated after various perturbations, including noise, aging and chemical insult. To our knowledge, this is the largest dataset of its kind for the inner ear. We are using this dataset to identify and select targets,

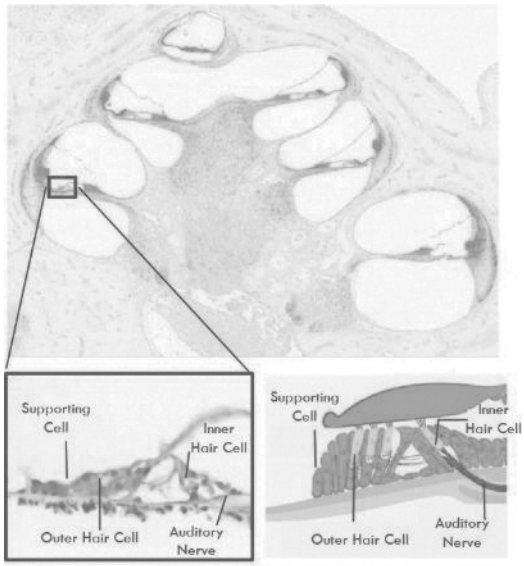
including reprogramming factors to promote inner ear hair cell regeneration, and cell-selective promoters to drive precise expression of transgenes and restore functionality in hair cells and non-sensory support cells of the inner ear.



Precision Gene Therapy and Proprietary, Cell-Selective Promoters

We have evaluated seven naturally occurring and engineered AAVs in non-human primate species and found that multiple AAV capsids reliably transduce a broad set of cell types within the inner ear. Notably, one of these AAV serotypes is AAV1, a well-studied and understood AAV serotype that is used in a gene therapy product approved by European regulatory authorities. The image below presents a cross-section of the cochlea of a non-human primate with red staining indicating AAV1 transduced cells at a dose of $3.2x10^{11}$ viral genomes per ear. The broad tropism we observed of AAV1 and other AAV capsids at modest doses in the non-human primate inner ear supports our belief that we can selectively target a large number of cell types within the human inner ear with naturally occurring AAV capsids when coupled with a cell-selective promoter. We believe that because of the broad tropism of these AAVs in human inner ear cells, therapeutics based on these AAVs may not require capsid engineering and thereby avoid potential manufacturing complications and safety concerns attributable to novel capsids.

Cross-section of the Non-human Primate Cochlea with AAV1 Transduced Cells



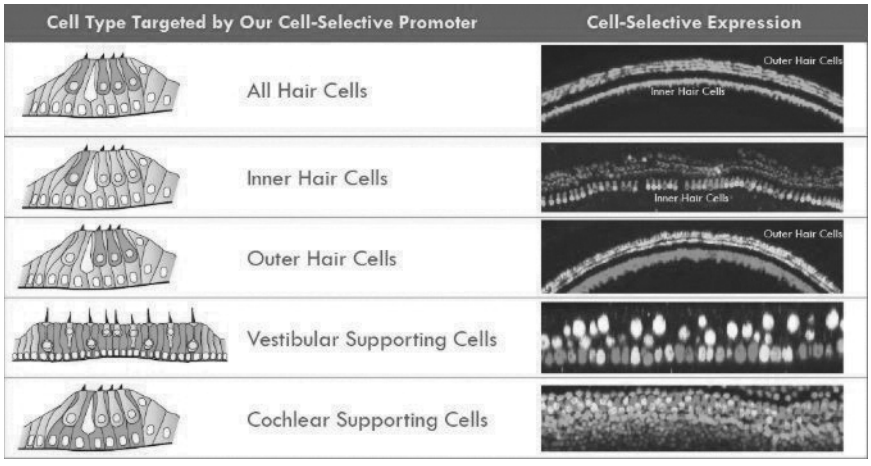
Sensory region containing inner and outer hair cells

The favorable transduction profile of multiple AAV capsids within the inner ear coupled with the enclosed compartment of the inner ear generally facilitates the use of a dual vector approach to deliver a full-length transgene, such as the OTOF gene in DB-OTO, that would normally exceed the packaging capacity of AAV vectors. We have evaluated multiple dual vector strategies and employ a proprietary dual-hybrid approach in which our two vectors enable expression of a full-length transgene.

Using proprietary analyses, we have exploited our single-cell genomics capabilities to develop a library of cell-selective promoters for therapeutically relevant cell types within the inner ear. Candidate promoters are designed based on gene expression, local epigenetic state and conservation across mammals, and we then validate each candidate across model systems and across species.

To date, we have generated and confirmed the specificity of cell-selective promoters that limit expression to therapeutically relevant inner ear cells in mice and non-human primates spatially and temporally. The image below shows representative images of green fluorescent protein, or GFP, a reporter gene used as a surrogate for a therapeutic transgene under the control of a cell-selective promoter. Based on our preclinical studies, we believe that cell-selective promoters could enable greater efficacy and durability and minimize potential toxicity in our gene therapies.

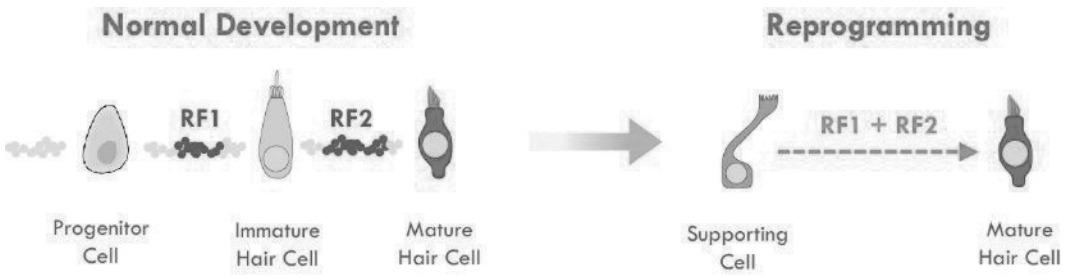
Cell-Selective Promoters in Therapeutically Relevant Inner Ear Cells



Reprogramming Factors to Control Cell Fate

Our regeneration strategy is to convert supporting cells, the cells adjacent to hair cells, into new hair cells in the inner ear. Our single-cell genomics and bioinformatics dataset includes hair cells at all stages of development, allowing us to reconstruct a differentiation trajectory that spans nascent hair cells to mature subtypes like inner and outer hair cells, and has enabled us to identify reprogramming factors that control cochlear and vestibular hair cell fate during normal development. Once identified, these can be expressed to reprogram supporting cells into new hair cells during adulthood. As shown in the image below, we identify candidate reprogramming factors expressed during the normal transition from progenitor cell to immature hair cell to mature hair cell, as represented by the figure on the left. We then evaluate the ability of those reprogramming factors to drive a mature hair cell fate via selective expression in inner ear supporting cells as shown by the figure on the right.

Reprogramming Factor Identification



Our Pipeline

Our portfolio of product candidates and programs is primarily derived from our proprietary platform and is focused in three areas:

- **Gene Therapies for Congenital, Monogenic Hearing Loss** designed to restore functional cells within the cochlea to address hearing disorders caused by single gene mutations
- **Gene Therapies for Hair Cell Regeneration** designed to replace lost hair cells within the inner ear to address acquired hearing loss and balance disorders
- **Otoprotection Therapeutic** in clinical development to prevent hearing loss in cancer patients undergoing chemotherapy with cisplatin

Gene Therapies for Congenital, Monogenic Hearing Loss

We are leveraging our platform to advance gene therapy programs designed to selectively replace genes for congenital, monogenic hearing loss. We are developing our lead gene therapy product candidate, DB-OTO, to provide durable, high quality, physiological hearing to individuals with profound, congenital hearing loss caused by mutations of the OTOF gene. In addition to DB-OTO, we are advancing additional gene therapy product candidates and programs targeting hearing loss resulting from other monogenic forms of hearing loss, including AAV.103, which aims to restore hearing in individuals with mutations in the GJB2 gene, AAV.104, which aims to restore hearing in individuals with mutations in the STRC gene and AAV.105, which aims to restore hearing in individuals with another single gene mutation. To date, over 90 distinct genes have been identified by researchers that lead to non-syndromic, congenital hearing loss when mutated. In approximately 80% of these cases, the hearing loss is autosomal recessive.

DB-OTO

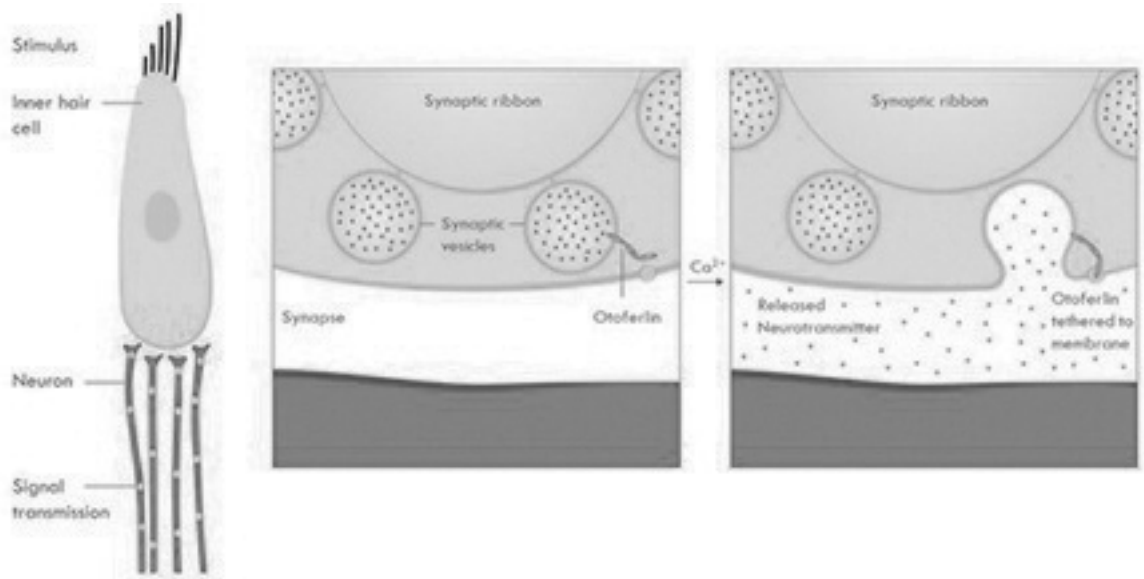
DB-OTO is an AAV-based dual-vector gene therapy product candidate designed to be administered a single time to selectively express functional OTOF in the inner hair cells of individuals with OTOF deficiency with the goal of enabling the ear to transmit sound to the brain and enable durable, physiological hearing. In October 2022, we received clearance from the FDA for our IND application to initiate CHORD™, a Phase 1/2 dose escalation clinical trial of DB-OTO in pediatric patients, and in January 2023, we received approval from the MHRA for our CTA for the trial.

OTOF-Related Hearing Loss

Mutations of the OTOF gene are one of the most common causes of genetic, congenital hearing loss, accounting for up to 8% of all cases. We estimate that the prevalence of profound hearing loss from OTOF deficiency in the United States and the major markets in Europe is approximately 20,000 individuals. In these regions and many other locations around the world, newborns with OTOF-mediated hearing loss are typically identified through routine hearing screening using ABR or OAE prior to being discharged from the birthing hospital. A newborn that fails an initial screen will typically be given a full diagnostic assessment, including genetic testing in some cases, as a follow-up to confirm the finding and to potentially identify the underlying cause of the hearing loss.

OTOF is a protein expressed in cochlear inner hair cells that enables communication between the sensory cells of the inner ear and the auditory nerve by regulating synaptic transmission. As shown in the image below, normal functioning OTOF enables inner hair cells to release neurotransmitters in response to stimulation by sound, which then activates the auditory nerve and carries the signal to the brain.

Functional OTOF Enables Inner Hair Cells To Release Neurotransmitters



Newborns born with mutations in the OTOF gene have fully developed structures within the inner ear. However, these newborns have profound hearing loss because signaling between the ear and the brain is disrupted. Importantly, despite OTOF deficiency, preclinical models and human clinical data suggest that the remainder of the inner ear and hearing circuit are fully functional. For example, while OTOF-deficient individuals present with an absent ABR, OAEs can still be detected, suggesting that the sensory cells within the inner ear remain viable and that expression of a functional OTOF gene could enable restoration of hearing.

There are currently no approved therapies to address OTOF-mediated hearing loss. The only available treatment options are assistive devices, such as a hearing aid or CI. Hearing aids provide very little benefit and are only used in a small minority of patients. CIs provide a clear benefit over profound hearing loss. However, they have significant limitations as they provide impoverished signals to the brain. Furthermore, the surgical implantation of a CI into the inner ear potentially makes the implant incompatible with future restorative therapies for that ear. Thus, we believe restoration of hearing would be transformative for these individuals.

Our Solution

DB-OTO is designed to provide durable, high quality, physiological hearing by expressing a functional OTOF gene directly in the hair cells that enable the ear to transmit sound to the brain. DB-OTO is a cell-selective AAV gene therapy that uses AAV1 as a delivery vehicle to facilitate expression of an OTOF transgene under the control of a proprietary Myosin15, or Myo15, promoter. OTOF is a large gene which exceeds the packaging capacity of an AAV vector. As a result, DB-OTO employs a dual vector approach involving the delivery of the transgene in two separate parts, with each part being delivered by a separate AAV vector and then combining through intracellular recombination to express a full length OTOF gene.

DB-OTO is intended to be administered a single time intracochlearly to patients using the surgical approach employed by neurotologists and pediatric otolaryngologists during a standard cochlear implantation procedure. This delivery is a well-accepted surgical approach for accessing the inner ear. We believe the cell-selective expression of OTOF under the Myo15 promoter and the established surgical procedure will provide competitive advantages important to the success of DB-OTO.

Clinical Development

In October 2022, we received clearance from the FDA for our IND application to initiate CHORD™, a Phase 1/2 dose escalation clinical trial of DB-OTO in pediatric patients, and in January 2023, we received approval from the MHRA for our CTA for the trial. The Phase 1/2 clinical trial is designed to evaluate the safety, tolerability and efficacy of DB-OTO in pediatric patients with congenital hearing loss due to an OTOF deficiency. In addition to safety and tolerability endpoints, established, clinically relevant, objective and behavioral measurements of hearing will be used as efficacy endpoints in the clinical trial. The auditory brainstem response, which was used to characterize the dose-response of DB-OTO after intra-cochlear delivery in translational animal studies, will serve as an early, objective, clinically accepted readout of hearing thresholds in the clinical trial. We expect the first two participants in the U.S. portion of the Phase 1/2 clinical trial will be as young as seven years of age and that subsequent participants will include children as young as two years of age and infants younger than two years of age. We expect to dose infants two years of age and younger in the U.K portion of the Phase 1/2 clinical trial. We have commenced trial site startup activities and expect to initiate the Phase 1/2 clinical trial of DB-OTO in the first half of 2023. We anticipate reporting the initial safety and tolerability data and preliminary efficacy data, as measured by ABR, from the first patients in the Phase 1/2 clinical trial in the first quarter of 2024.

To further support our Phase 1/2 clinical trial, we are conducting a natural history study in collaboration with Hospital Ramon y Cajal in Spain, which utilizes a database that currently is comprised of 149 patients with OTOF mutations. Data from this study were presented at the 2022 Midwinter Meeting of the Association for Research in Otolaryngology and highlighted the unmet medical need associated with OTOF deficiency. We are establishing similar collaborations at additional sites in the United States and within Europe, each of which will involve collection of physiologic, behavioral and patient-reported experience endpoints that may be used to guide our clinical development plans for DB-OTO and other gene therapy programs for congenital hearing loss. We believe the conduct and results of these natural history studies will also encourage diagnostic practices at clinical trial sites to support patient identification for our Phase 1/2 clinical trial of DB-OTO and our other gene therapy programs for congenital hearing loss. We have also launched Amplify, a sponsored testing program. Through this program, Prevention Genetics is performing genetic testing using one of its comprehensive gene panels in eligible patients with auditory neuropathy at collaborating sites. We believe this testing program will provide a greater understanding of genetic sensorineural hearing loss and will promote enrollment in our future clinical trials.

We have been granted orphan drug designation and rare pediatric disease designation by the FDA for DB-OTO for the treatment of patients with OTOF-related, congenital hearing loss and plan to seek fast track designation for DB-OTO.

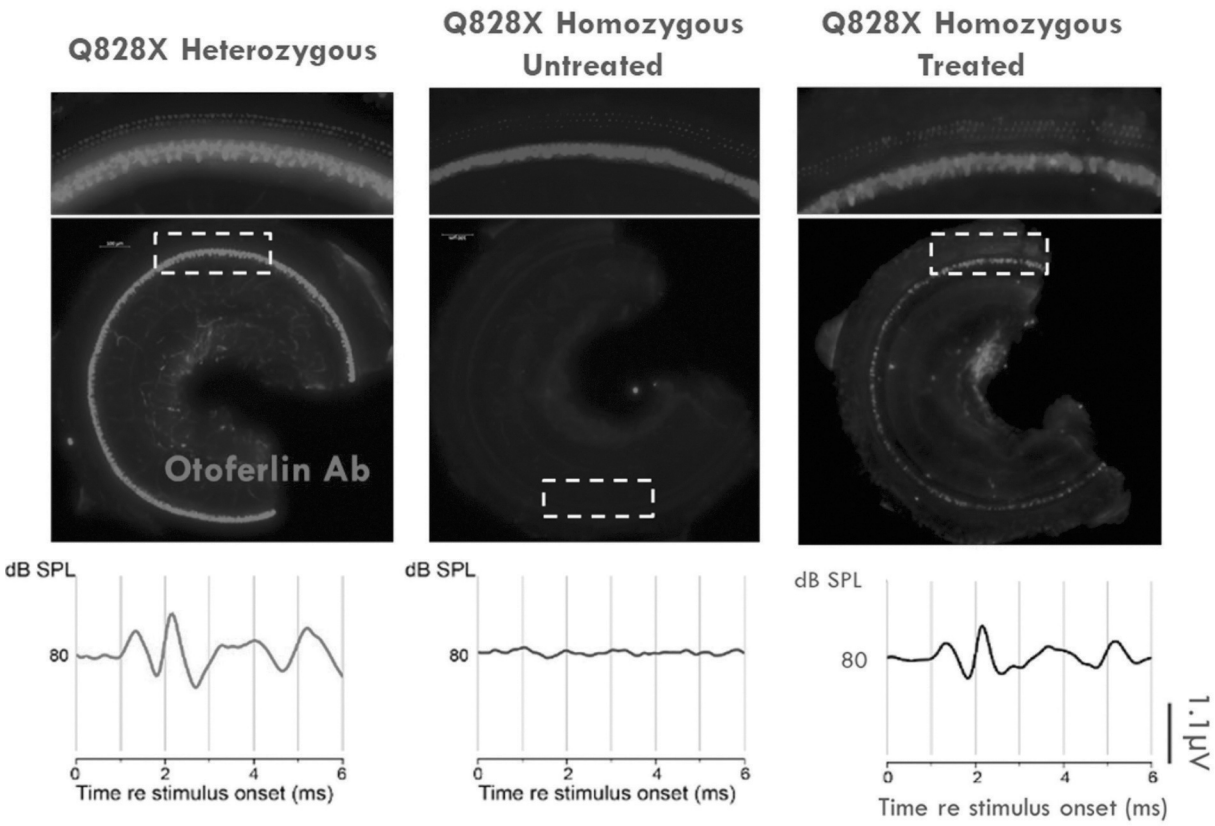
Preclinical Studies

The feasibility of restoring functional hearing in a mouse model of OTOF-deficiency has been established in a number of independent, academic studies. For example, researchers from the University of California, San Francisco and the University of Florida utilized a dual vector approach to deliver two different recombinant vectors directly to the cochlea of OTOF knockout mice. In that study, a single intracochlear injection of the vector pair in a fully developed mouse ear was able to generate the full length OTOF gene, express OTOF protein in the inner hair cells and restore hearing indistinguishable from wildtype, as measured by ABR.

In developing DB-OTO, we generated a novel knock-in mouse model that has a nonsense mutation, Q828X, commonly seen in individuals with OTOF-related hearing loss. We refer to the mice in the model as Q828X mice. We have used this model to conduct multiple preclinical studies of DB-OTO. For instance, we have conducted preclinical studies using this model to assess OTOF expression and the restoration of ABR waveforms. As shown by the representative image in the leftmost panel below, in this model, heterozygous mice with one mutant OTOF and one functional copy of the OTOF gene expressed OTOF protein in inner hair cells, as shown by the pink cells in the highlighted box, and a normal ABR waveform, shown in red, in response to an 80 dB sound pressure level, or SPL, stimulus. An 80 dB stimulus is equivalent to a gasoline-powered lawn mower. We observed similar ABR waveforms across 12 heterozygous mice and expression of OTOF across 12 heterozygous mice. As shown by the representative image in the middle panel below, in untreated Q828X mice with two mutant copies of OTOF, no OTOF protein can be visualized within the cochlea, as seen by the lack of pink cells in the highlighted box, and the ABR waveform, shown in blue, is undetectable in response to an 80 dB stimulus. We observed similar ABR waveforms in seven untreated Q828X mice and expression of OTOF across 16 untreated Q828X mice. Consistent with previous academic studies, and as shown in the representative image in the rightmost panel below, treatment with a pair of recombinant AAV vectors expressing two parts of the OTOF transgene that was delivered by a single intracochlear injection resulted in expression of functional OTOF protein within the cochlea of the Q828X mice, as shown by

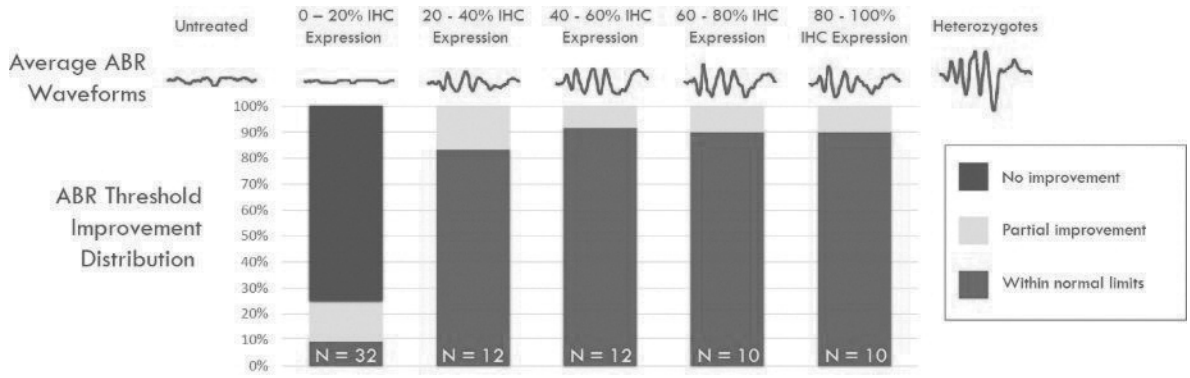
the pink cells in the highlighted box, and restoration of normal ABR waveforms, as shown by the black trace. Furthermore, in these mice, we observed restoration of normal ABR waveforms in a fully developed mouse ear up to 12 months of age. We observed similar ABR waveforms and expression of OTOF across 13 studies of treated Q828X mice.

Preclinical Studies Demonstrated Restoration of Hearing in Mouse Model with Dual AAV-OTOF



Because the anatomy of the inner ear, an accessible, small, enclosed compartment, enables direct delivery of high viral titers, we believe that dual vector approaches are able to generate sufficient levels of full-length transcript within the cochlea. In preclinical studies, across AAV-OTOF injections in Q828X mice, we have observed that achieving OTOF expression in greater than 20% of inner hair cells was sufficient to restore ABR sensitivities within normal ranges. In these studies, we evaluated 76 Q828X mice that were between ten weeks and 44 weeks of age at time of hearing assessment and histology for OTOF-positive inner hair cell counts. As shown in the chart below, we observed that in those mice with OTOF expression in fewer than 20% of inner hair cells, 75% showed no recovery of ABR sensitivity, 16% showed some improvement of ABR sensitivity and 9% showed ABR sensitivity within the normal range. In those mice with OTOF expression in 20% or greater of inner hair cells, all showed some improvement in ABR sensitivity, including 83% to 92% that had ABR sensitivities within the normal range. For purposes of this analysis, normal range indicates the mean plus or minus two standard deviations we observed in untreated heterozygous mice. ABR sensitivity for both heterozygous controls and treated OTOF-deficient animals was recorded in response to a 22 kHz stimulus, which we believe represents a mid-to-high cochlear frequency location in mice that may translate to a frequency important for perception of human speech.

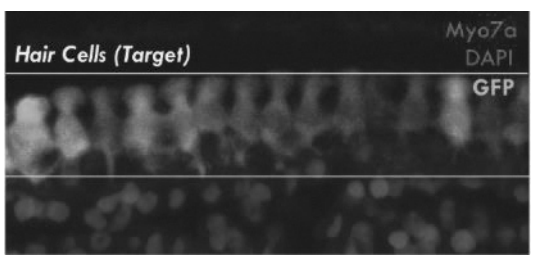
Expression of OTOF in Greater than 20% of Inner Hair Cells Restored Normal ABR Sensitivity in Q828X Mice



We have evaluated in several preclinical studies, including dose-response studies, the dependence of OTOF expression and functional recovery on dosing increments at one month-post DB-OTO infusion. In these studies, we administered by intracochlear injection DB-OTO in doses that ranged from $1.4x10^{10}$ to $1.9x10^{11}$ viral genomes per ear to 189 mice that were four to eight weeks of age. At these ages, the inner ear was fully developed and is expected to replicate translational conditions for future treatment in infants and young children. Over the dosing range, we observed a pronounced dose response in which low dosing resulted in minimal OTOF expression and minimal recovery of ABR sensitivity while mid-to-high doses resulted in a higher percentage of inner hair cells expressing OTOF and meaningful recovery of ABR sensitivity across vocalization frequency ranges for the mice. Using DB-OTO manufactured using our proposed clinical grade manufacturing process, we have demonstrated a dose response in the Q828X model over a 10-fold range. In wild type mice that were also dosed over this same 10-fold range with DB-OTO manufactured using our proposed clinical grade manufacturing process, we also observed good tolerability as assessed by the ABR. These findings, along with a volumetric scaling approach, were used to inform dose selection for our exploratory safety and distribution studies in Q828X mice and non-human primates, as well as the design of our good laboratory practice, or GLP, toxicology studies and planned human clinical trials.

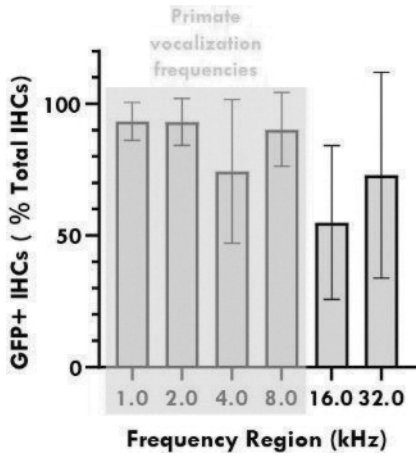
Because we have observed that AAV capsids transduce a broad set of cell types within the inner ear, the use of AAV capsids to deliver therapy necessitates strategies to minimize toxicity associated with expression of OTOF in cells that do not typically express OTOF. To address this concern, we leveraged our molecular insights and capabilities to identify and engineer a Myo15 cell-selective promoter to control transgene expression such that OTOF is expressed only in hair cells. We have observed this selectivity in multiple preclinical studies in mice and non-human primates. In one study, to evaluate translation of DB-OTO, we delivered by intracochlear injection dual vectors encoding GFP in which the GFP complementary DNA is split between two AAV vectors under the control of the Myo15 promoter to the inner ears of six non-human primates. In the study, our dual vector technology dosed at $2.0x10^{12}$ viral genomes per ear was able to drive highly selective expression of GFP in the majority of hair cells of the non-human primate inner ear. The image below presents a representative section of the non-human primate inner ear in which GFP, shown in green, is present only in hair cells, the cells located between the dotted white lines and identified with the hair cell marker Myo7a. Nuclei of hair cells and other cells are shown in blue, as stained by DAPI, a fluorescent stain that binds strongly to DNA.

Dual Vector AAV and Myo15 Drove Highly Selective Expression of GFP in Hair Cells of Non-Human Primates



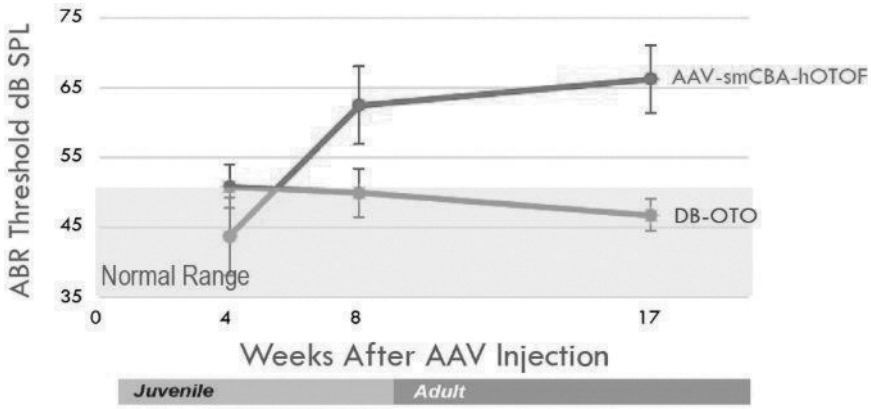
The fraction of inner hair cells expressing dual vector GFP was assessed at several different frequencies across the six non-human primates in the study. In frequency regions we believe to be important for non-human primate vocalization, we observed expression of GFP in greater than 75% of inner hair cells as highlighted in the graph below.

Dual Vector AAV and Myo15 Drove Full Length GFP Expression in Most Inner Hair Cells of Non-Human Primates Across Frequency Regions



To compare durability of hearing restoration between OTOF expressed by our cell-selective promoter, Myo15, and a ubiquitous promoter, smCBA, we conducted a preclinical study in 15 Q828X mice with DB-OTO or AAV-smCBA-hOTOF, respectively, and followed their recovery over a seventeen-week period. In this study, we administered DB-OTO by intracochlear injection. We measured ABR in response to frequency-specific tones intended to activate specific regions of the cochlea, as well as in response to gross broadband click stimuli which activate multiple frequencies. In the study, we observed that ABR waveforms were restored within four weeks following injection with DB-OTO and were maintained through week seventeen as measured in response to frequency-specific stimuli. While we also saw initial functional recovery with the ubiquitous promoter at four weeks post-infusion, we observed that the response to frequency-specific stimuli had deteriorated when measured at eight weeks post-treatment. The image below shows ABR thresholds in response to 22 kHz stimulus with the blue trace depicting DB-OTO treated mice and the red trace depicting AAV-smCBA-hOTOF treated mice.

Durability of ABR Sensitivity with DB-OTO Compared to AAV Vector with a Ubiquitous Promoter in Q828X Mice



When hearing in this study was assessed by gross broadband click stimuli spanning multiple frequencies, the test was less sensitive to this loss of durability. Histological analysis revealed degeneration of inner hair cells throughout the cochlea after treatment using the ubiquitous promoter, which was pronounced in specific regions. Importantly, this loss of function was not observed in the Q828X mice that were infused with DB-OTO. Taken together, we believe that these observations support our belief that cell-selective regulation of expression may provide significant advantages in the development of gene therapies for the durable restoration of hearing.

To further understand the improvement in durable restoration of hearing with our hair cell-selective promoter, in a separate study, we delivered DB-OTO and the same comparison vector by intracochlear injection to a total of 40 wild type and heterozygous carriers of the Q828X mutations to assess impacts on hearing. We found that DB-OTO had no negative impact on hearing as measured by ABR in response to frequency-specific tones or gross broadband click stimuli in the heterozygous mice. Histological analysis revealed normal inner hair cells up to one month after DB-OTO infusion. By contrast, we observed loss of inner hair cells throughout the cochlea and loss of hearing for frequency specific ABR tone

responses after infusion of the comparison vector under the control of the ubiquitous promoter. Of note, we again observed that this gross broadband click response was less sensitive to the distributed pathology that we observed.

Preclinical Safety

We performed GLP toxicology studies to support the conduct of human clinical trials of DB-OTO. In these studies, we used OTOF-deficient mice and wild type non-human primates to characterize the pharmacology, toxicity and biodistribution of DB-OTO after inner ear delivery. In the studies involving non-human primates, we modeled the surgical approach and delivery of DB-OTO that we plan to use in our Phase 1/2 clinical trial.

We quantified human OTOF mRNA transcript levels and observed that they peaked four weeks after DB-OTO injection in mice and six weeks after DB-OTO injection in non-human primates, plateauing thereafter. A similar time course was observed for ABR improvements post DB-OTO injection in the congenitally deaf rodent model. We followed Q828X mice for eight months post-administration of DB-OTO and observed stability of the instated ABR throughout that period at therapeutically active doses.

In our GLP studies, we did not observe any adverse DB-OTO-related findings in otic or non-otic tissues across any evaluation in Q828X mice or non-human primates. We also assessed the distribution of vector genomes and human OTOF mRNA expression outside of the ear following DB-OTO injection in non-human primates. We observed limited vector distribution into peripheral tissues and limited vector shedding in non-human primates. Human OTOF mRNA expression was shown to be restricted to the cochlea at 27 weeks, supporting the selectivity of the promoter and the potential ability to drive sustained human OTOF transgene expression.

The proposed volumetric dose scaling was directly proportional to the total cochlea perilymph volumes of mouse, non-human primate and humans. Comparable vector genome DNA and human OTOF mRNA levels in mouse and non-human primate GLP studies provided additional supporting evidence for the validity of this volumetric scaling approach for dose adjustments of DB-OTO between these species.

In our preclinical studies, the presence of pre-existing neutralizing antibodies was not associated with an impact on transgene expression in the ear or safety post DB-OTO injection, suggesting that there may be limited impact of systemic pre-existing neutralizing antibodies on local administration of AAV gene therapies to the inner ear.

AAV.103, AAV.104 and AAV.105

We believe that additional autosomal recessive mutations that result in congenital hearing loss can potentially be addressed by AAV gene replacement therapies. We are designing AAV.103 to restore hearing to individuals with a GJB2 deficiency, the most common cause of congenital hearing loss. Most GJB2 mutations result in severe-to-profound hearing loss, and we estimate the prevalence in the United States and the major markets in Europe is at least 280,000 individuals. GJB2 encodes the connexin 26 gap junction protein, which is expressed in non-sensory cells of the inner ear such as supporting cells. Connexins are a family of transmembrane proteins that form channels between adjacent cells. Gap junction channels are believed to be involved in the recycling of ions, such as potassium, to maintain the electric voltage needed to enable normal hearing. We are designing AAV.103 to selectively express GJB2 in only the cells that normally express GJB2, a strategy we believe could potentially restore gap junctions and restore hearing. Using our single-cell genomics capabilities, we have identified the sequence of the GJB2 promoter and a promoter/enhancer combination that selectively limited expression of a reporter gene in preclinical studies of mice. We have identified a product candidate for our AAV.103 program. We are continuing to conduct preclinical efficacy experiments, which we expect to inform the potential clinical development plan. We are working in collaboration with Regeneron to develop AAV.103.

We are designing AAV.104 to restore hearing to individuals with an STRC deficiency, the second most common cause of autosomal recessive, non-syndromic, congenital hearing loss. We estimate that the prevalence of individuals with this form of hearing loss in the United States and the major markets in Europe is approximately 70,000. STRC is a large, extracellular, structural protein expressed in outer hair cells of the cochlea. Functional outer hair cells amplify sound within the ear, a process required for normal hearing sensitivity and frequency selectivity. AAV.104 is designed to express STRC selectively in outer hair cells, thus providing STRC specifically in its natural cellular location. We believe this strategy has the potential to restore expression of the protein and hearing in individuals with an STRC deficiency. We have identified the sequence of the STRC promoter and observed that it is selective for outer hair cells in preclinical studies of mice and nonhuman primates. We are currently conducting preclinical studies in our AAV.104 program to evaluate preclinical efficacy. We are working in collaboration with Regeneron to develop AAV.104.

Beyond AAV.103 and AAV.104, we are designing AAV.105 to restore hearing in individuals with another single gene mutation. We are independently working on AAV.105, and AAV.105 is not subject to our collaboration with Regeneron.

Gene Therapies for Hair Cell Regeneration

We are leveraging our platform to advance gene therapy programs to regenerate inner ear hair cells for acquired hearing and balance disorders. Our vestibular hair cell regeneration program aims to restore balance in patients with BVP by regenerating lost hair cells within the vestibule. We also have an additional gene therapy program that aims to treat acquired hearing loss by regenerating cochlear outer hair cells.

Vestibular Hair Cell Regeneration

We are designing AAV-based gene therapies that utilize a proprietary vestibular supporting cell-selective promoter to express ATOH1, a transcription factor required for hair cell differentiation, alone or in combination with reprogramming factors, in vestibular supporting cells to promote the regeneration of vestibular hair cells. We are developing this program, which includes DB-ATO and AAV.201, for the treatment of BVP. In February 2023, we presented new preclinical data from our vestibular regeneration efforts at the Association for Research in Otolaryngology.

Bilateral Vestibulopathy

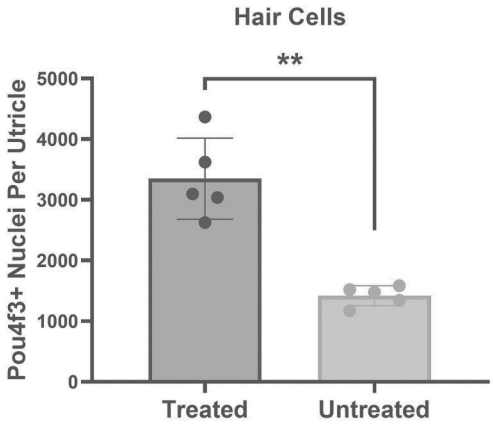
BVP is a debilitating condition that is often caused by certain antibiotics such as gentamicin. Patients with BVP may experience dramatic loss of hair cells and have difficulty maintaining a stable gaze and posture. These individuals have a 70% incidence of oscillopsia, or blurred vision during head movement, and may experience chronic disequilibrium and postural instability. Most patients with BVP are unable to work due to disability and are at a 31-fold increased risk of falls. Many BVP patients lack vestibular hair cells, yet retain vestibular supporting cells and neurons, which we believe makes them amenable to a regenerative approach. We estimate there are approximately 130,000 adults with BVP in the United States and the major markets in Europe. Despite the severity, there are no approved therapies for BVP, and the standard of care is focused on rehabilitation and lifestyle changes that do not address the underlying loss of vestibular hair cells often responsible for the condition.

Our Solution

Our vestibular hair cell regeneration programs aim to restore balance by promoting regeneration of hair cells in the vestibule within the inner ear. The intended mechanism of action is direct conversion of vestibular supporting cells into vestibular hair cells through expression of ATOH1, alone or in combination with reprogramming factors. ATOH1 is a well-studied gene within the inner ear field as it is both necessary and sufficient to generate hair cells during development. In a number of published, independent preclinical studies, ATOH1 has been shown to convert adult vestibular supporting cells into vestibular hair cells. We have evaluated multiple AAV capsids in preclinical studies to assess their ability to reliably transduce vestibular supporting cells in both mice and non-human primates. Because many patients with BVP have normal hearing, in order to minimize any impact on hearing, we intend to utilize an AAV capsid in combination with a selective promoter to limit cochlear expression. In multiple preclinical studies, we have observed that the promoters under consideration, for example the human SLC6A14 promoter, were selective for vestibular supporting cells when delivered by intravestibular injection to the adult mouse and non-human primate ear in vivo.

We have developed two mouse models of BVP in which we can selectively ablate vestibular hair cells in vivo without killing vestibular supporting cells. In a preclinical study in these mice, as quantified in the image below, intravestibular delivery of AAV with an ATOH1 transgene under control of the human SLC6A14 promoter resulted in selective expression of ATOH1 in vestibular support cells and regeneration of vestibular hair cells in the utricle, as measured by the hair cell marker Pou4f3. Similar results were observed in the crista, one of the semicircular end organs of the vestibular system.

In Vivo Regeneration of Vestibular Hair Cells in Utricle in Mouse Model of BVP Following Delivery of ATOH1



We applied our single-cell genomics and bioinformatics capabilities to characterize the newly generated hair cells in the study and confirmed that their transcriptional profiles resembled mature vestibular hair cells. We also evaluated preclinical efficacy in vivo using behavioral assays but did not observe significant functional recovery. We are continuing to evaluate whether ATOH1 expression alone might be sufficient to restore lost vestibular function. In parallel, we are currently conducting preclinical studies in our mouse models of BVP to explore whether a single AAV vector delivered with an intravestibular injection expressing a combination of ATOH1 and reprogramming factors may further enhance maturation of specific vestibular hair cell types. We believe this combination may enable superior restoration of balance in patients with BVP.

Loss of hair cells in the vestibular system can also result from the aging process, which may lead to chronic balance problems and result in significant life impairment and an increased risk of falls. We believe that our strategy of regenerating vestibular hair cells through conversion of neighboring supporting cells could restore balance, and we may explore whether any product candidate we develop for BVP is able to regenerate vestibular hair cells as a treatment for acquired age-related and other balance disorders.

Cochlear Hair Cell Regeneration

Age-related hearing loss and noise-induced hearing loss affect millions of people in the United States and Europe. Research has shown that the degree of hearing loss in these populations is best predicted by the amount of cochlear hair cell loss. We believe that restoring cochlear hair cells could restore hearing in these individuals. In our cochlear hair cell regeneration program, we are designing an AAV-based gene therapy that utilizes cell-selective expression of reprogramming factors to convert supporting cells into cochlear hair cells. We are currently conducting preclinical studies to evaluate the feasibility of our approach.

Otoprotection Therapeutic

We are developing DB-020 for the prevention of cisplatin-induced hearing loss in cancer patients receiving chemotherapy. DB-020 is a novel formulation of STS, a naturally occurring metabolite which inactivates cisplatin through covalent binding. We have optimized the DB-020 formulation for local delivery to the ear, which we believe may enable DB-020 to protect hearing without impacting the beneficial effect of cisplatin chemotherapy. We have completed a Phase 1 clinical trial of DB-020 in Australia and are conducting a randomized, double-blind, placebo-controlled, multicenter Phase 1b clinical trial to evaluate the safety and efficacy of DB-020 in preventing hearing loss in cancer patients undergoing chemotherapy with cisplatin. In June 2022, we reported positive topline data from an interim analysis of the ongoing Phase 1b clinical trial and ceased enrollment. We are in the safety follow-up portion of the clinical trial, which we anticipate completing in the first half of 2023. The FDA has granted fast track designation for DB-020 for the prevention of cisplatin-related ototoxicity.

Cisplatin-Induced Hearing Loss

Cisplatin is systemically delivered and one of the most commonly used chemotherapeutics despite severe, dose-limiting side effects. Ototoxicity is one of the most common, serious adverse effects of cisplatin-based chemotherapy, leading

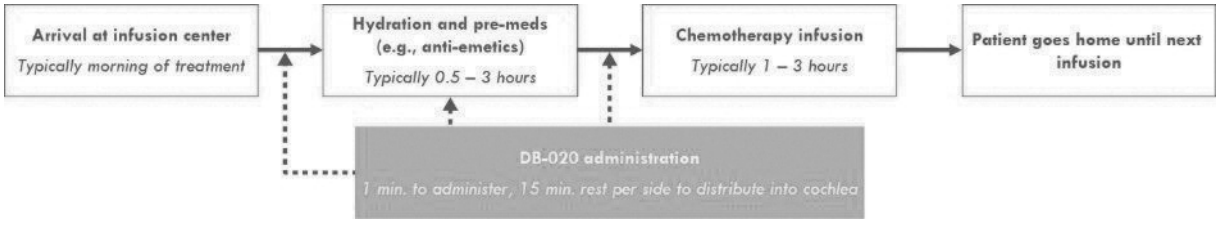
to permanent hearing loss in the majority of patients. We estimate that approximately 270,000 patients per year in the United States, the major markets in Europe and Japan receive cisplatin-based chemotherapy with more than 85% of these patients receiving high doses that correlate to a greater risk to hearing. This hearing loss can be devastating and is often associated with imbalance, tinnitus and a debilitating sensitivity to sound. Oncologists indicate that cisplatin is commonly used with curative intent, suggesting that protecting patients' quality of life after chemotherapy is of high concern to both physicians and patients. Due to the irreversible nature, we believe that prophylactic use of DB-020 could benefit patients receiving cisplatin.

Multiple third-party Phase 3 clinical trials in pediatric patients have shown prevention of ototoxicity associated with cisplatin through inactivation of cisplatin by STS. In the most recent trial, intravenous infusion of STS reduced the incidence of ototoxicity by nearly 50%. To mitigate the risk that systemic delivery of STS concurrent with cisplatin infusion would inactivate cisplatin throughout the body and prevent or reduce the beneficial chemotherapeutic effect, administration of STS in this trial was delayed until six hours post-treatment with cisplatin. Importantly, even in the context of delayed systemic administration of STS, a negative impact on overall survival was observed in patients with metastatic disease, suggesting that eventual use in pediatric patients would need to be limited to those with localized, non-metastatic solid tumors.

Our Solution

We are developing DB-020 as a formulation of STS to be delivered to the inner ear to mitigate cisplatin-induced ototoxicity in patients of all ages. To accomplish this, we formulated DB-020 to achieve high cochlear concentrations of STS following a local injection through the ear drum, or transtympanically, into the middle ear. Transtympanic administration is a brief, minimally invasive, routine, office-based procedure performed by ENTs and is generally well-tolerated. As highlighted in the image below, we believe DB-020's route of administration and pharmacologic profile allows for flexible timing at multiple points in the typical chemotherapy patient workflow and can be administered at any point in the three hours prior to receiving cisplatin.

Potential Timeline for Administration of DB-020 to Patients Receiving Cisplatin



Clinical Trials

In 2019, we completed a randomized, double-blind, placebo-controlled Phase 1 clinical trial of DB-020 to assess safety in healthy volunteers in Australia. In the Phase 1 clinical trial, a total of 32 subjects were randomized to receive one of four doses of DB-020 or placebo in one ear. Ten additional subjects were randomized to receive bilateral doses, or doses in both ears, of DB-020 or placebo. In the trial, DB-020 was well-tolerated with adverse events generally mild to moderate. There were no serious treatment-emergent adverse events, or TEAEs, study drug-related serious TEAEs, discontinuations due to TEAEs, or deaths in the trial. Notably, administration of DB-020 resulted in only nominal systemic increases of STS, which we believe suggests that DB-020 should have no impact on the efficacy of cisplatin therapy throughout the body. The maximal thiosulfate concentration above endogenous levels ranged from 0.80 to 2.45 μM. In preclinical, in vitro studies in five human cancer cell lines, we determined that DB-020 concentrations less than or equal to 30 μM did not reduce cisplatin anti-tumor or cell-killing.

Based on the results of our Phase 1 clinical trial, we submitted an IND for DB-020 to the FDA and initiated a randomized, double-blind, placebo-controlled, multicenter Phase 1b clinical trial of DB-020 in patients undergoing treatment with cisplatin in 2019. In June 2022, we reported topline data from an interim analysis of the ongoing Phase 1b clinical trial. Patients enrolled in the Phase 1b clinical trial were randomized to receive one of two doses of DB-020 in one ear while the contralateral ear received placebo, enabling each patient to serve as their own control. Patients were administered DB-020 and placebo up to three hours prior to each cisplatin infusion. Consistent with the results of the Phase 1 clinical trial, data from the interim analysis demonstrated that DB-020 was well tolerated, with mostly mild to moderate adverse events and no significant safety issues observed. Furthermore, DB-020 administered prior to cisplatin had no apparent effect on systemic cisplatin levels. In the data from the interim analysis, 13 of 17 (76.5%) patients experienced cisplatin-induced ototoxicity in the placebo ear after the first cycle of cisplatin; 15 of 17 (88.2%) patients experienced cisplatin-induced ototoxicity in the

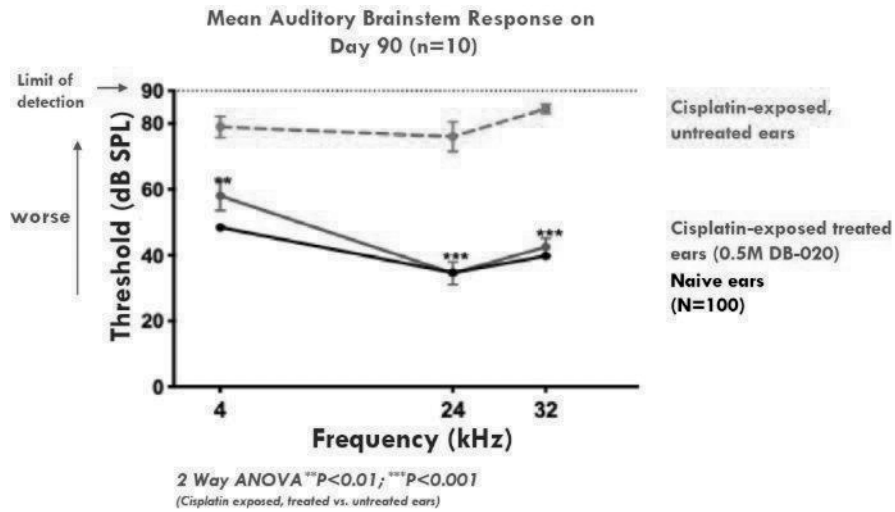
placebo ear by the last evaluable test. Ototoxicity was defined according to the American Speech-Language-Hearing-Association criteria for significant ototoxic change. Placebo-treated ears lost approximately 30dB on average from baseline in high frequencies, shifting patients from normal or slight hearing loss to moderate hearing loss (two hearing loss categories) on average. In the 15 patients who experienced ototoxicity in the placebo ear by the last evaluable test, DB-020 protected 13 (87%) from ototoxicity in their DB-020-treated ear. Eight of 15 (53.3%) were completely protected, and five of 15 (33.3%) were partially protected. Complete protection was defined as no change in hearing from baseline in the ear that received DB-020 according to the ASHA ototoxicity criteria in the clinically assessed range. Ears treated with DB-020 lost approximately 8dB on average from baseline. DB-020 reduced cisplatin-induced loss of speech audibility by 80% as measured by the Speech Intelligibility Index, suggesting treatment with DB-020 may reduce the risk of needing assistive hearing devices after receiving cisplatin.

We ceased enrolling patients in our Phase 1b clinical trial of DB-020, following our announcement of the positive interim analysis results from the first 19 patients enrolled in the trial. Patients who remain in the study have completed the treatment portion of the study and are being followed for safety follow up activities, which we anticipate completing in the first half of 2023. We plan to report additional data from the interim analysis in 2023, and we are working with key opinion leaders to integrate learnings from the interim analysis into an updated clinical development plan. We expect to consult with regulatory agencies in 2023 as part of that planning. We are considering a range of potential approaches by which to advance DB-020, including entering into strategic collaborations for the further development and commercialization of DB-020. The FDA has granted fast track designation for DB-020 for the prevention of cisplatin-related ototoxicity.

Preclinical Studies

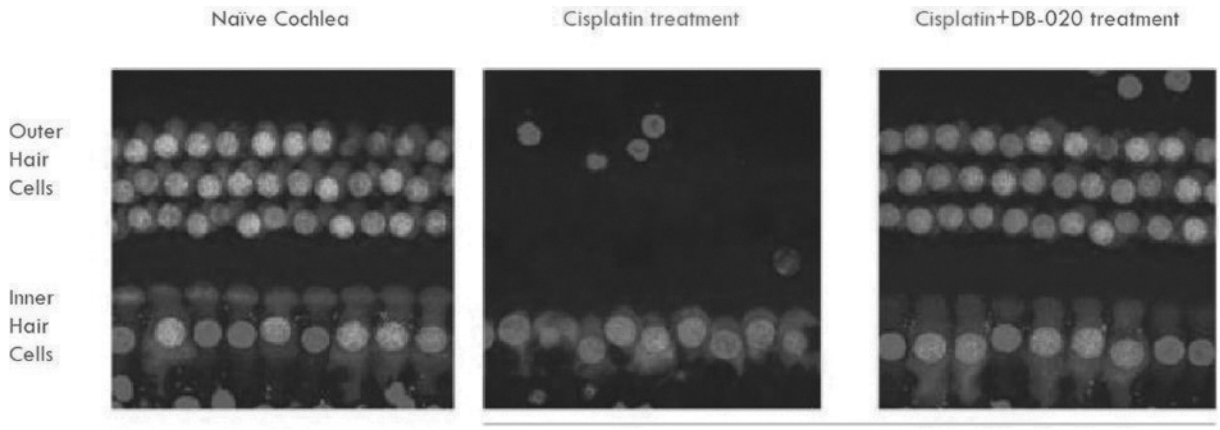
To assess the potential efficacy of DB-020, we established four rodent models of cisplatin-induced ototoxicity. In preclinical studies in these models, cisplatin treatment alone resulted in profound hearing loss in the rodents and histological analyses demonstrated significant loss of outer hair cells, while treatment with DB-020 by local injection one hour before and one hour after treatment with cisplatin resulted in protection of hearing and outer hair cells. As shown in the blue trace in the image below, treatment with 0.5M of DB-020 at one hour after cisplatin injection resulted in almost complete hearing protection as measured by ABR across a range of frequencies in every rodent tested in one of our models, while rodents exposed to cisplatin alone experienced profound hearing loss as shown in the red trace in the image below.

Mean Auditory Response Across Frequencies for Cisplatin-Exposed Rodents Treated with DB-020



As shown in the representative image below taken seven days after intervention, histological analyses also revealed outer hair cells were protected in rodents treated with DB-020.

Histological Analysis of Outer Hair Cells in Cisplatin-Exposed Rodents Treated with DB-020



In pharmacokinetic experiments conducted in a total of 40 rodents, cochlear concentrations above the predicted minimal efficacious dose persisted for 16 hours after injection. Importantly, local delivery minimized systemic exposure of STS to within the range of endogenous plasma levels.

Manufacturing

Gene Therapies

We believe the inner ear is particularly well suited for gene therapy treatments as its small, enclosed nature and accessibility for direct, local delivery facilitate efficient transduction of target cells with a small volume of viral vectors. For a given product, we believe we will only need to deliver a small volume and low dose of vector to achieve near-complete transduction of the target cells in the cochlea or vestibule. As such, we expect that the manufacturing requirements for our inner ear gene therapies will be significantly lower than systemically delivered gene therapies or gene therapies that target larger organs.

Due to the expected AAV tropism for inner ear cell types, we plan to utilize naturally occurring AAV serotypes for which third party manufacturers have clinical and manufacturing experience. Accordingly, our production process utilizes an approach with HEK293 mammalian cells and transient plasmid transfection, a commonly used host cell and approach for many clinical and commercial AAV gene therapies that are familiar to global regulatory agencies. Commercial raw materials and reagents are readily available from multiple third-party suppliers.

Our relationship with Regeneron provides us access to established, research-stage AAV capabilities. We believe working with an experienced contract development and manufacturing organization, or CDMO, with an extensive history of clinical and commercial AAV expertise will enable rapid development of our lead gene therapy product candidate, DB-OTO. We have established a relationship with Catalent Maryland, Inc. (formerly Paragon Bioservices, Inc), a CDMO, to perform process development and current good manufacturing practices, or cGMP, manufacturing for DB-OTO. We have completed technology transfer and process development at Catalent, and Catalent has manufactured cGMP clinical material of DB-OTO to support the Phase 1/2 clinical trial. Catalent has significant AAV development experience through to commercial manufacturing and has produced over 100 clinical GMP batches across multiple third-party programs utilizing the same production platform approach that was used for the manufacture of DB-OTO.

We believe that manufacturing expertise and capacity is of critical importance for the development of gene therapies, and we intend to continue to work with and rely upon CDMOs for production of future gene therapies. We also plan to continue to evaluate our options for ensuring manufacturing capacity on an ongoing basis, including strategic partnerships, contractual relationships with other CDMOs, as well as investment in internal manufacturing.

Small Molecules

Our DB-020 product candidate is a proprietary formulation of STS optimized for local delivery to the ear for which we utilize well-established manufacturing and drug-delivery technologies developed by the pharmaceutical industry for small molecule manufacturing. We rely on third-party contract manufacturers and contract research organizations with a track record of FDA-compliant manufacturing and testing for the drug product. After appropriate testing and meeting

specifications, we release these materials to additional contract manufacturers for packaging into finished drug product for clinical use.

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business, including by seeking, maintaining and defending patent rights, 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 our field. 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.

Our future commercial success depends, in part, on our ability to: obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our intellectual property rights, in particular our patents rights; preserve the confidentiality of our trade secrets and operate without infringing, misappropriating or violating the valid and enforceable patents and proprietary rights of third parties. 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.

The patent positions of biotechnology and pharmaceutical companies like ours are generally uncertain and can involve complex legal, scientific and factual issues. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. We also cannot ensure that patents will issue with respect to any patent applications that we or our licensors may file in the future, nor can we ensure that any of our owned or licensed patents or future patents will be commercially useful in protecting our product candidates and methods of manufacturing the same. In addition, the coverage claimed in a patent application may be significantly reduced before a patent is issued, and its scope can be reinterpreted and even challenged after issuance. As a result, we cannot guarantee that any of our products will be protected or remain protectable by enforceable patents. Moreover, any patents that we hold may be challenged, circumvented or invalidated by third parties. See "Risk Factors—Risks Related to Our Intellectual Property" for a more comprehensive description of risks related to our intellectual property.

We generally file patent applications directed to our key programs in an effort to secure our intellectual property positions vis-a-vis these programs. Additionally, we file patent applications and in-license patents and patent applications directed to our platform, our product candidates, our programs, which includes gene therapies and related technology, methods and other related technologies. As of March 1, 2023, our owned, co-owned and in-licensed patent estate included four U.S. granted patents, 15 pending U.S. non-provisional patent applications, 76 foreign pending patent applications, seven pending Patent Cooperation Treaty, or PCT, applications and five pending U.S. provisional patent applications.

Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office, or USPTO, may be significantly narrowed before issuance, if issued at all. We expect this may be the case with respect to some of our pending patent applications referred to below.

DB-OTO

With regard to our DB-OTO product candidate, we co-own with Regeneron three pending U.S. non-provisional patent applications and 19 pending foreign patent applications with claims directed to compositions of matter covering DB-OTO and methods of use thereof. These applications and patent applications claiming the benefit of the PCT application, if issued, are expected to expire in 2040, without giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We also own two pending U.S. non-provisional patent applications, one pending PCT application, six pending foreign patent applications, and one pending U.S. provisional patent application with claims directed to compositions of matter covering DB-OTO and methods of use thereof. These applications and patent applications claiming the benefit of the PCT application or the provisional application, if issued, are expected to expire in 2039, 2042, and 2044, without giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We also exclusively license from the Regents of the University of California, and exclusively license from University of Florida, a patent family co-owned by University of Florida and Regents of the University of California comprised of a pending U.S. application with claims directed to methods of increasing expression of OTOF and eight pending foreign patent applications in such jurisdictions as Australia, China, Europe, and Japan, which if issued, are expected to expire in 2038, assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We also exclusively license from the University of Missouri a U.S. patent with claims directed to a hybrid dual vector system such as

the system used in DB-OTO, which is expected to expire in 2030, without giving effect to any potential patent term extension assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees.

DB-020

With regards to our DB-020 product candidate, we own three granted U.S. patents with claims directed to pharmaceutical compositions covering our DB-020 product candidate or methods of mitigating hearing loss using DB-020, which are expected to expire in 2039, without giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We also own a pending U.S. patent application and 12 corresponding pending foreign patent applications in such jurisdictions as Australia, Brazil, Canada, China, Europe, and Japan, with claims directed to pharmaceutical compositions and methods of their use, which if issued, are expected to expire in 2039, assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We also own a pending U.S. non-provisional patent application with claims directed to methods of mitigating hearing loss using DB-020, which if issued, is expected to expire in 2039, without giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees, and 11 pending foreign patent applications in such jurisdictions as Australia, Brazil, Canada, China, Europe, and Japan. The foreign patent applications, if issued, are expected to expire in 2040, without giving effect to any potential patent term extensions and patent term adjustments and assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees.

Our Platform

The patent portfolio for our integrated, propriety platform includes patents and patent applications relating to our gene therapy for hair cell regeneration programs, our gene therapies for congenital, monogenic hearing loss, our gene therapy technologies, our cell-selective promoters and our formulations. Our platform portfolio is based upon our owned patent portfolio that includes patents and patent applications directed generally to the compositions of matter, pharmaceutical compositions, and methods of delivering and using the same. As of March 1, 2023, we owned or co-owned 37 pending U.S., PCT and foreign patent applications and one foreign granted patent covering components of our platform, including our cell-selective promoters. While we believe that the specific and generic claims contained in our pending applications provide protection for our platform, third parties may nevertheless challenge such claims in our patents. If any such claims are invalidated or rendered unenforceable for any reason, we will lose valuable intellectual property rights and our ability to prevent others from competing with us would be impaired. Any U.S. or ex-U.S. patents that may issue from pending applications that we control, if any, for our platform are projected to have a statutory expiration date in between 2039 and 2043, excluding any additional term for patent term adjustments or patent term extensions, if applicable.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the United States, the term of a patent covering an FDA-approved drug may, in certain cases, be eligible for a patent term extension under the Hatch-Waxman Act as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years, but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. It is possible that issued U.S. patents covering the use of products from our intellectual property may be entitled to patent term extensions. If our use of drug candidates or the drug candidate itself receive FDA approval, we intend to apply for patent term extensions, if available, to extend the term of patents that cover the approved use or drug candidate. We also intend to seek patent term extensions in any jurisdictions where available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such extensions should be granted, and, even if granted, the length of such extensions.

In addition to patent protection, we rely upon confidential know-how and continuing technological innovation to develop and maintain our competitive position. However, confidential know-how is difficult to protect. We seek to protect our proprietary information, in part, using confidentiality agreements with any collaborators, scientific advisors, employees and consultants and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. These agreements may not provide meaningful protection. These agreements may also be breached, and we may not have an adequate remedy for any such breach. In addition, our confidential know-how may become known or be independently developed by a third party or misused by any collaborator to whom we disclose such information. Despite any measures taken to protect our intellectual property,

unauthorized parties may attempt to copy aspects of our products or obtain or use information that we regard as proprietary. Although we take steps to protect our proprietary information, third parties may independently develop the same or similar proprietary information or may otherwise gain access to our proprietary information. As a result, we may be unable to meaningfully protect our proprietary information.

Our commercial success will also depend in part on not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our drugs or processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize our future drugs may have an adverse impact on us. If third parties have prepared and filed patent applications prior to March 16, 2013 in the United States that also claim technology to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of inventions.

Trademark Protection

As of March 1, 2023, we owned 48 U.S. and international trademark applications and registrations related to our business. We plan to register trademarks in connection with our products.

License and Collaboration Agreements

We are a party to a number of agreements under which we license patents, patent applications and other intellectual property from and/or collaborate with third parties. These agreements impose various diligence and financial payment obligations on us. We consider the following agreements to be material to our business.

License and Collaboration Agreement with Regeneron Pharmaceuticals, Inc.

In November 2017, we entered into a license and collaboration agreement, which was amended in October 2020 and February 2023, with Regeneron, or the Regeneron Agreement. The Regeneron Agreement had an original research term of five years and granted Regeneron the right to extend the research term for up to two years in one-year intervals. In November 2021, Regeneron exercised its right to extend the research term by one year to November 2023. The Regeneron Agreement is focused on the discovery and development of new potential therapies directed to a set of defined collaboration targets. We are currently developing DB-OTO, AAV.103 and AAV.104 in collaboration with Regeneron under the Regeneron Agreement. In October 2020, we entered into the first amendment to the Regeneron Agreement pursuant to which, among other things, ATOH1, the target of our DB-ATO program, was removed as a collaboration target and the terms and plans for the DB-OTO and AAV.103 programs were modified. We issued 10,000,000 shares of our Series C preferred stock to Regeneron in consideration for its entry into the first amendment to the Regeneron Agreement, which shares converted into 791,439 shares of our common stock upon the consummation of our initial public offering. In February 2023, we further amended the collaboration with Regeneron to provide for accelerated development milestone payments by Regeneron to us for clinical development milestones for DB-OTO and pre-IND milestones for AAV.103.

Pursuant to the Regeneron Agreement, during the research term, we have established research plans that specify the activities each party undertakes with respect to the discovery or development of therapies directed to specific collaboration targets, which we refer to as collaboration products. Each party is responsible for its own respective costs and has agreed to use commercially reasonable efforts to complete the activities as designated in the agreed-upon research plan. For the DB-OTO program, we have also committed to utilize a specified level of research personnel in the program. Additional collaboration targets may be added to the Regeneron Agreement by mutual consent or if they arise from certain novel target identification activities conducted under the Regeneron Agreement and achieve mutually agreed validation criteria. As between the parties, we are primarily responsible for the direction and conduct of the research program, however, Regeneron contributes various technologies and expertise of its own as well as employees and research services by mutual agreement. A joint research committee oversees the research program.

A joint product committee oversees development and commercialization of a collaboration product following IND acceptance for such collaboration product. As between the parties, we are solely responsible for developing and commercializing collaboration products in the field of hearing loss and balance disorders. We have an obligation to use commercially reasonable efforts to develop and commercialize such collaboration products in the field. During the term of the Regeneron Agreement, neither we nor Regeneron may develop or commercialize any products directed to collaboration targets in the field of treatment and prevention of disease involving loss of hearing or balance, other than pursuant to the Regeneron Agreement.

Pursuant to the Regeneron Agreement, Regeneron paid us an upfront fee of $25.0 million and purchased 12,500,000 shares of our Series B preferred stock at price per share of $2.00, which shares converted into 989,299 shares of our common stock upon the consummation of our initial public offering. In November 2021, Regeneron exercised its right to extend the research term for one-year to November 15, 2023. Regeneron paid us the extension fee of $10.0 million in the fourth quarter of 2022. If Regeneron elects to extend the term of the research program for an additional year, it will be obligated to pay us an additional $10.0 million for the final one-year extension. On a collaboration-product-by-collaboration-product basis, upon achievement of pre-defined milestones which begin at initiation of manufacturing to support GLP toxicology studies and conclude at initiation of a Phase 2 clinical trial, Regeneron is obligated to pay us milestone payments up to $35.5 million in aggregate if the collaboration product is a biologic or up to $33.5 million in the aggregate if the collaboration product is a small molecule. Such milestone payments are intended to reflect approximately half of the total cost needed to achieve the next milestone. From and after the initiation of a registration enabling trial, unless Regeneron decides to opt-out, we have agreed to split development and regulatory costs with Regeneron on an equal basis through the registration enabling trials.

Under the Regeneron Agreement, we are required to pay Regeneron tiered royalties on the worldwide net sales of collaboration products at percentages which range from mid-single digit to mid-thirties, with the exact royalty rate depending on the extent to which Regeneron shared in the funding of the collaboration product, the level of net sales of the collaboration product, the nature of any intellectual property contributed by Regeneron included in the collaboration product and whether the product is sold inside or outside the field. In the case of collaboration products for which Regeneron does not opt-out, our obligation to pay tiered royalties on the worldwide net sales ranges from percentages in the mid-twenties to mid-thirties. In the case of collaboration products for which Regeneron opts-out, our obligation to pay tiered royalties on the worldwide net sales ranges from percentages in the mid-single digits to mid-twenties. Our obligation to make royalty payments to Regeneron on account of worldwide net sales of collaboration products continues so long as we, our affiliates, licensees or sublicensees sell collaboration products. To date, we have not made any royalty or other payments to Regeneron under the Regeneron Agreement.

Pursuant to the Regeneron Agreement, we have granted to Regeneron a right of first negotiation if we choose to license or otherwise transfer rights to develop or commercialize collaboration products. Regeneron may opt-out of the collaboration with respect to any collaboration product following submission of the IND to the FDA for a collaboration product: immediately prior to the initiation of a registration enabling trial, immediately prior to the submission of a marketing authorization application and at any time following the initiation of the registration enabling trial, upon notice to us within a specified time period. If Regeneron opts out with respect to a collaboration product, it does not owe further milestones on that collaboration product and will no longer share development expenses for such collaboration product. Regeneron may opt back into a collaboration product under certain circumstances.

Pursuant to the first amendment to the Regeneron Agreement, Regeneron agreed to pay us $0.3 million to fund our ongoing research program and $0.5 million to help secure the services of a CDMO. The $0.5 million payment is creditable against the milestone associated with the initiation of manufacturing to support GLP toxicology studies of DB-OTO. Additionally, Regeneron agreed to reimburse us for up to $10.5 million of third-party costs related to the GLP toxicology studies of DB-OTO as such costs are incurred and paid by us, and we agreed that the aggregate potential milestone payments for DB-OTO would be reduced by $15.0 million. In addition, notwithstanding its removal from the collaboration, for DB-ATO, we agreed to pay to Regeneron a royalty calculated as a low- to mid-single digit percentage of net sales of DB-ATO, on a country-by-country basis, until the latest of the expiration of the last patent covering DB-ATO in such country, the expiration of all applicable regulatory exclusivities for DB-ATO in such country and the tenth anniversary of the first commercial sale of DB-ATO in such country. Through December 31, 2022, we had received an aggregate of $5.5 million in milestone payments from Regeneron pursuant to the collaboration.

The term of the Regeneron Agreement will continue until neither we nor any of our affiliates nor any of our sublicensees is developing or commercializing any collaboration products. Either party may terminate the agreement for cause for the other party's uncured material breach on prior written notice, if the other party becomes insolvent or in certain circumstances in which either party challenges the patent rights of the other party. In addition, if we suspend development activities for a specified period of time, or if we fail to invest specified levels of committed resources to the DB-OTO program, Regeneron would have certain remedies, including the ability to obtain control over further development and commercialization of DB-OTO and AAV.103, subject to payments to us to be negotiated, and the ability to terminate its obligations to us with respect to other collaboration products.

License Agreements with The Regents of The University of California and the University of Florida Research Foundation, Incorporated

We are a party to license agreements with each of The Regents of The University of California, or UCSF, and University of Florida Research Foundation, Incorporated, or UFRF, pursuant to which we separately and independently

license from each institution patent rights they jointly own related to compositions and methods for expressing OTOF, which cover DB-OTO, our product candidate for profound hearing loss due to an otoferlin deficiency.

License Agreement with The Regents of The University of California

In October 2019, we entered into a license agreement with UCSF relating to certain patent rights related to compositions and methods for expressing OTOF, which we refer to as the UCSF License.

Under the UCSF License, we acquired an exclusive, sublicensable, worldwide license to make, have made, use, sell, offer for sale and import products, services, and methods covered by the licensed patent rights, and to perform licensed processes. Under the UCSF License, UCSF retains the right to make, use and practice certain of the licensed intellectual property rights for research and educational purposes, and the right to license to other academic and nonprofit organizations to practice the patent rights for research and educational purposes. The UCSF License is also subject to pre-existing rights of the U.S. government and the NIH.

In connection with our entry into the UCSF License, we paid to UCSF a small upfront fee and agreed to pay UCSF an additional small fee following the issuance of the first patent under the UCSF License. In addition, under the terms of the UCSF License, we are required to pay to UCSF certain nominal annual license maintenance fees unless we are selling or otherwise exploiting licensed products or services paying royalties to UCSF on net sales for such licensed products or services. With respect to such royalty obligations, we agreed to pay UCSF low single-digit royalties on annual net sales of licensed products and services. Our obligation to pay royalties continues until the expiration or abandonment of the last of the patent rights licensed under the UCSF License. In addition, we are obligated to make contingent milestone payments to UCSF totaling up to $500,000 upon the achievement of certain regulatory milestones and up to $5.0 million upon the achievement of certain commercial sales milestones whether achieved by us or a sublicensee of ours. In the event that we sublicense the licensed patent rights, UCSF is also entitled to receive a percentage of the sublicensing income received by us.

In addition, if we grant a sublicense under our license from UCSF, we are also required to concurrently grant a sublicense under the UCSF License on the terms and conditions of the UCSF License.

Under the UCSF License, we are obligated to diligently proceed with the development, manufacture and sale of at least one licensed product and/or service, and to earnestly and diligently market such licensed product and/or service after receipt of any requisite regulatory approvals and in quantities sufficient to meet market demand. We have also agreed to meet specified development, regulatory and commercialization milestones for the licensed patent rights by specified dates, subject to extensions that may be granted by UCSF under certain circumstances. For example, we agreed to dose the first subject in a clinical trial for a licensed product by September 30, 2023. UCSF has the right to revoke our right to sublicense the UCSF License or reduce the license to a nonexclusive license if we are unable to perform our diligence obligations.

The agreement will continue until the last to expire or abandonment of the patent rights under the UCSF License. The patent rights we have licensed under the UCSF License are expected to expire in 2038, assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We may terminate the agreement by providing prior written notice to UCSF or we may terminate the rights under patent rights on a country-by-country basis by giving notice in writing to UCSF. UCSF has the right to terminate the agreement if we fail to make any payments, challenge any UCSF patent rights or otherwise materially breach the agreement and fail to cure such breach within a specified grace period.

License Agreement with University of Florida Research Foundation

In October 2020, we entered into a license agreement with UFRF, which was amended in June 2022 and March 2023, relating to certain patent rights related to compositions and methods for expressing OTOF, which we refer to collectively as the UFRF License.

Under the UFRF License, we acquired an exclusive, sublicensable, worldwide license to make, have made, use, sell, have sold, and import products covered by the licensed patent rights. Under the UFRF License, UFRF retains the right for itself and any non-profit institution or governmental entity to practice and have practiced certain of the licensed intellectual property rights for research, clinical, and educational purposes. The UFRF License is also subject to pre-existing rights of the U.S. government.

In connection with our entry into the UFRF License, we paid to UFRF an upfront fee of $100,000 and agreed to pay UFRF an additional $100,000 following the issuance of the first patent under the UFRF License. In addition, under the terms of the UCSF License, we are required to pay to UFRF certain nominal annual license maintenance fees until the first year in which we sell a licensed product. Under the UFRF License, we have agreed to pay UFRF a low single-digit royalty on annual net sales of licensed products. Our obligation to pay royalties continues on a licensed-product-by-licensed-product and country-by-country basis until the expiration of the last of the patent rights licensed under the UFRF License. In addition, we are obligated to make contingent milestone payments to UFRF totaling up to $800,000 in the aggregate upon the achievement

of certain clinical and regulatory milestones and up to an additional $11,150,000 in the aggregate upon the achievement of certain commercial sales milestones, in each case, whether achieved by us or by a sublicensee of ours. In the event that we sublicense the licensed patent rights, UFRF is also entitled to receive a percentage of the sublicensing revenue received by us.

Under the UFRF License, we are obligated to use commercially reasonable efforts to develop, commercialize and maintain supply of licensed product. We have also agreed to meet specified development, regulatory and commercialization milestones for the licensed patent rights by specified dates, subject to extensions that may be granted by UFRF under certain circumstances. Our milestone relating to dosing the first subject in a clinical trial for a licensed product by March 31, 2023 was modified to initiating our Phase 1/2 clinical trial of DB-OTO by June 30, 2023. UFRF has the right to terminate our license if we fail to perform our diligence obligations.

The agreement will continue on a licensed-product-by-licensed-product and country-by-country basis until the last to expire of the patent rights under the UFRF License. The patent rights we have licensed under the UFRF License are expected to expire in 2038, assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We may terminate the agreement by providing prior written notice to UFRF. UFRF has the right to terminate the agreement if we fail to make any payments, bring action or proceeding against UFRF or otherwise breach the agreement and fail to cure such breach within a specified grace period. In addition, the agreement will immediately terminate upon certain events of insolvency of either party.

License Agreement with The Curators of the University of Missouri

In August 2019, we entered into a license agreement with The Curators of the University of Missouri, or the University of Missouri, which was amended in February 2021, May 2022 and March 2023 relating to certain patent rights related to the AAV vectors we are using in the gene therapies we are developing for congenital, monogenic hearing loss due to an OTOF deficiency and due to a deficiency in another specified gene, which we refer to collectively as the University of Missouri License.

Under the University of Missouri License, we acquired an exclusive license to make, have made, use, sell, have sold, import, distribute or otherwise transfer products, or the licensed products, covered by the licensed patent rights. We may sublicense the licensed patent rights with the University of Missouri's prior written approval. Under the University of Missouri License, the University of Missouri retains the right to make, use and practice certain of the licensed intellectual property rights for non-commercial research purposes and the right to license to nonprofit, academic or government institutions the patent rights for non-commercial research purposes. The University of Missouri License is also subject to pre-existing rights of the U.S. government and the NIH.

In connection with our entry into the University of Missouri License, we paid to the University of Missouri an upfront fee of $100,000 and agreed to pay the University of Missouri a nominal annual license maintenance fee. In addition, we agreed to pay to the University of Missouri a low single-digit royalty on annual net sales of licensed products sold regardless of where such licensed products are manufactured and an additional low single-digit royalty on annual net sales of licensed products that are sold outside of the United States but manufactured within the United States, with a specified minimum annual royalty requirement. Our obligation to pay royalties continues until the expiration or abandonment of the last of the patent rights licensed under the University of Missouri License. In addition, we are obligated to make milestone payments on a licensed-product-by-licensed-product basis to the University of Missouri totaling up to $772,500 in the aggregate upon the achievement of certain development and regulatory milestones and up to $13.1 million in the aggregate upon the achievement of certain commercial sales milestones, whether achieved by us or a sublicensee of ours. In the event that we sublicense the licensed patent rights, the University of Missouri is also entitled to receive a tiered percentage of the sublicensing revenue received by us, which varies depending on the stage of development at which we enter into such sublicense.

Under the University of Missouri License, we are obligated to use reasonable commercial efforts to advance the licensed product towards commercialization. We have also agreed to meet specified development, regulatory and commercialization milestones for the licensed patent rights by specified dates. Our milestone relating to dosing the first subject in a clinical trial for a licensed product by March 31, 2023 was modified to initiating our Phase 1/2 clinical trial of DB-OTO by June 30, 2023. We paid less than $0.1 million to the University of Missouri with respect to a milestone that became payable upon our submission of an IND application for DB-OTO. The University of Missouri has the right to unilaterally terminate the University of Missouri License or reduce the license to a nonexclusive license if we fail to meet such specified milestones.

The agreement will continue until the last to expire or abandonment of the patent rights under the University of Missouri License. The patent rights we have licensed under the University of Missouri License are expected to expire in 2030, without giving effect to any potential patent term extension assuming payment of all appropriate maintenance, renewal, annuity or other governmental fees. We may terminate the agreement by providing prior written notice to the University of

Missouri or upon the uncured material breach of the agreement by the University of Missouri. The University of Missouri has the right to terminate the agreement if we fail to make any payments, upon the occurrence of certain events of insolvency for us, challenge any University of Missouri patent rights or otherwise materially breach the agreement and fail to cure such breach within a specified grace period.

Commercialization

We plan to directly market and commercialize our lead gene therapy product candidate, DB-OTO, if approved in the United States and Europe, by developing our own sales and marketing force, targeting ENTs and audiologists. Outside of these regions and for any other product candidates that may be approved, we intend to establish marketing and commercialization strategies for each as we approach potential approval and expect to be able to leverage our then-existing sales and marketing force. We believe that the benefits of a strategic collaboration could be particularly valuable to us with respect to the further development and commercialization of DB-020 and intend to evaluate such opportunities on the basis of the clinical data we generate in our ongoing Phase 1b clinical trial of DB-020.

Competition

We face competition from a wide array of companies in the pharmaceutical, specialty pharmaceutical, biotechnology and medical device industries that have products or programs focused on hearing or balance disorders. We may also compete with the intellectual property, technology and product development efforts of academic, governmental and other public and private research institutions.

Our competitors, which include both small companies and large companies, may have significantly greater financial resources, an established presence in the market, a longer operating history than us and greater expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement, and marketing approved products than we do. Smaller or earlier-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific, sales, marketing, and management personnel, establishing clinical trial sites and patient registration for clinical trials and potentially acquiring technologies complementary to, or necessary for, our programs.

The key competitive factors affecting the success of any products that we commercialize are likely to be their efficacy, safety, convenience, price and the availability of reimbursement from government and other third-party payors. Our commercial opportunity for any of our product candidates could be reduced or eliminated if our competitors develop and commercialize products that are more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop. Our competitors also may obtain approval from the FDA or other regulators for their products before we may obtain approval for ours, which may result in regulatory exclusivity, and may commercialize products before we are able to.

Hearing Loss

We expect that our product candidates and programs for congenital, monogenic hearing loss and for acquired hearing loss will compete with product candidates and programs being advanced by:

- Akouos, Inc., which is developing AK-OTOF, a gene therapy for profound hearing loss resulting from deficiency in OTOF, which is in clinical development, and has preclinical gene therapy programs targeting GJB2 and Usher Syndrome Type 3A and for treatment of sensorineural hearing loss through hair cell regeneration. Akouos, Inc. received clearance of its IND for AK-OTOF in September 2022. In December 2022, Eli Lilly and Company acquired Akouos, Inc.; and
- Sensorion SA, or Sensorion, which has three gene therapy programs targeting GJB2-mediated hearing loss, Usher Syndrome Type I and OTOF-deficiency in preclinical development. Sensorion has announced that it plans to submit a CTA within Europe for its OTOF-GT program in the first half of 2023.

We are aware of PEDMARK, a formulation of sodium thiosulfate delivered via systemic injection, developed by Fennec Pharmaceuticals, Inc. that in September 2022 received FDA approval for use to reduce the risk of ototoxicity associated with cisplatin in pediatric patients one month of age and older with localized, non-metastatic solid tumors. We are also aware of product candidates in development, including SENS-401, a small molecule being developed by Sensorion that is in Phase 2 clinical trials for prevention of chemotherapy related hearing loss, D-methionine, an amino acid that has been shown to protect against hearing loss in experimental settings, and SPI-3005, an oral agent primarily being developed by

Sound Pharmaceuticals, Inc. for noise and age-related hearing loss that is in Phase 2 clinical trials for chemotherapy related hearing loss. We are also aware of additional therapeutic approaches in preclinical development that may target prevention of hearing loss in patients receiving cisplatin chemotherapy. We are also aware that Sound Pharmaceuticals, Inc. is pursuing treatments for Meniere's Disease, a balance disorder.

Balance Disorders

We are aware of other companies developing product candidates for balance disorders, including Sound Pharmaceuticals, Inc. which is pursuing treatments for Meniere's Disease.

Government Regulation

Government authorities in the United States, at the federal, state and local levels, and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, licensing, packaging, storage, record-keeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting and import and export of pharmaceutical products. The processes for obtaining marketing 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.

Regulation of Drugs and Biologics in the United States

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug and Cosmetic Act, or FDCA, and implementing regulations. Biologic products, including gene therapy products, are licensed for marketing under the Public Health Service Act, or PHSA, and regulated under the FDCA and implementing regulations. Both drugs and biologics are also subject to other federal, state and local statutes and regulations. We, along with our vendors, collaboration partners, clinical research organizations, or CROs, clinical trial investigators, and CDMOs will be required to navigate the various preclinical, clinical, manufacturing and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates.

A drug candidate must be approved by the FDA through an NDA. A biological product candidate is licensed by FDA through a biologics license application, or BLA. A company, institution or organization that takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor. A sponsor seeking approval to market and distribute a new product in the United States must typically undertake the following:

- completion of extensive preclinical laboratory tests, animal studies and formulation studies in compliance with applicable regulations, including the FDA's GLP regulations and standards and other applicable regulations;
- design of a clinical protocol and submission to the FDA of an IND application for human clinical testing, which must take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the drug product for each proposed indication and the safety, potency and purity of the biological product candidate for each proposed indication;
- preparation and submission to the FDA of an NDA or BLA after completion of all pivotal clinical trials;
- review by an FDA advisory committee, if applicable;
- satisfactory completion of FDA pre-approval inspections of the manufacturing facility or facilities at which the proposed product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the clinical trial sites that generated data in support of the NDA or BLA to assure compliance with GCP requirements and the integrity of the clinical data;
- payment of user fees for FDA review of the NDA or BLA;

- FDA review and approval of the NDA or BLA to permit commercial marketing of the product for particular indications for use in the United States; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and any post-approval studies required by the FDA.

Preclinical Studies

Before a sponsor begins testing a compound with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of chemistry, toxicity and formulation, purity and stability, as well as in vitro and animal studies to assess the potential safety and activity of the product candidate for initial testing in humans and to establish a rationale for therapeutic use. These studies are generally referred to as IND-enabling studies. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations and standards and the U.S. Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application.

The IND

An IND is an exemption from the FDCA that allows an unapproved product to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved application. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical studies. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical studies, together with manufacturing information, analytical data and any available clinical data or literature to support the use of the investigational product and plans for clinical trials, among other things, are submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. The IND will become effective automatically 30 days after receipt by the FDA, unless the FDA raises concerns or questions about the conduct of the trials as outlined in the IND prior to that time and imposes a clinical hold on the IND or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. The FDA may nevertheless initiate a clinical hold after the 30 days if, for example, significant public health risks arise.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical, nonclinical, and/or chemistry, manufacturing, and controls. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so.

Human Clinical Trials in Support of a Marketing Application

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease or condition to be treated under the supervision of qualified principal investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, inclusion and exclusion criteria of subjects, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the trial complies with certain regulatory requirements of the FDA in order to use the trial as support for an IND or application for marketing approval. Specifically, the FDA requires that such trials be conducted in accordance with GCP, including review and approval by an independent ethics committee and informed consent from participants. The GCP requirements encompass both ethical and data integrity standards for clinical trials. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical trials, as well as the quality and integrity of

the resulting data. They further help ensure that non-IND foreign trials are conducted in a manner comparable to that required for clinical trials in the United States.

Further, each clinical trial must be reviewed and approved by an IRB, either centrally or individually, at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, the safety of human subjects and the possible liability of the institution. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completion. An IRB must operate in compliance with FDA regulations. The FDA, IRB, or sponsor may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or that the participants are being exposed to an unacceptable health risk. There also are requirements governing the reporting of ongoing clinical trials and completed clinical trials to public registries. In the United States, information about applicable clinical trials, including clinical trial results, must be submitted within specific timeframes for publication on the www.clinicaltrials.gov website. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board, or DSMB. This group provides authorization for whether or not a study may move forward at designated check points based on certain available data from the trial to which only the DSMB has access. Finally, under the NIH Guidelines for Research Involving Recombinant DNA Molecules, or the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may be required after approval. These phases generally include the following:

- Phase 1 clinical trials are initially conducted in a limited population of healthy volunteers or patients with the target disease or condition to test the product candidate for safety, dose tolerance, absorption, metabolism, distribution, excretion, pharmacodynamics and, if possible, to gain early evidence of effectiveness.
- Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials.
- Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is found to be potentially effective and that the product candidate has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a product; such Phase 3 studies are referred to as "pivotal."

A clinical trial may combine the elements of more than one phase and the FDA often requires more than one Phase 3 trial to support marketing approval of a product candidate. A company's designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Generally, pivotal trials are Phase 3 trials, but they may be Phase 2 trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In December 2022, with the passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, actions plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of products approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase 4 clinical trial requirement or to request a change in the product labeling. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA within 15 calendar days after the sponsor determines that the information qualifies for reporting for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product candidate; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within 7 calendar days after the sponsor's initial receipt of the information.

Finally, sponsors of clinical trials are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Both the NIH and the FDA have recently signaled the government's willingness to begin enforcing those requirements against non-compliant clinical trial sponsors. The failure to submit clinical trial information to clinicaltrials.gov, as required, is a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. Although the FDA has historically not enforced these reporting requirements due to the U.S. Department of Health and Human Services', or HHS, long delay in issuing final implementing regulations, those regulations have now been issued and the FDA has issued several Notices of Noncompliance to manufacturers since April 2021.

Manufacturing and Other Regulatory Requirements

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the drug or biological characteristics of the product candidate and finalize a process for manufacturing the drug product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and manufacturers must develop, among other things, methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life and to identify appropriate storage conditions for the product candidate.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Inspections must follow a "risk-based schedule" that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated. The PREVENT Pandemics Act, which was enacted in December 2022, clarifies that foreign drug manufacturing establishments are subject to registration and listing requirements even if a drug or biologic undergoes further manufacture, preparation, propagation, compounding, or processing at a separate establishment outside the United States prior to being imported or offered for import into the United States.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, a marketing application or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The sponsor, the FDA and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the sponsor may request an amendment to the plan at any time.

For products intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of a sponsor, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than 90 days after FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law requires the FDA to send a Pediatric Research Equity Act, or PREA, Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although the FDA has recently taken steps to limit what it considers abuse of this statutory exemption.

Special Regulations and Guidance Governing Gene Therapy Products

The FDA has defined a gene therapy product as one that mediates its effects by transcription or translation of transferred genetic material or by specifically altering host genetic sequences, such as products that include nucleic acids, or genetically engineered microorganisms, engineered site-specific nucleases used for human genome editing and ex vivo genetically modified human cells. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient. Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. Within the CBER, the review of gene therapy and related products is consolidated in the Office of Tissues and Advanced Therapies, and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise the CBER on its reviews.

The FDA has issued various guidance documents regarding gene therapies, including recent final guidance documents released in January 2020 relating to chemistry, manufacturing, and controls information for gene therapy INDs, long-term follow-up after the administration of gene therapy products and gene therapies for rare diseases. Although the FDA has indicated that these and other guidance documents it previously issued are not legally binding, compliance with them is likely necessary to gain approval for any gene therapy product candidate. The guidance documents provide additional factors that the FDA will consider at each stage of development and relate to, among other things: the proper preclinical assessment of gene therapies; the chemistry, manufacturing, and control 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 for potential delayed adverse effects in participants who have received investigational gene therapies with the duration of follow-up based on the potential for risk of such effects. For AAV vectors specifically, the FDA typically recommends that sponsors continue to monitor participants for potential gene therapy-related adverse events for up to a five-year period.

For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with Good Tissue Practices, or GTP. These standards are found in FDA regulations and guidance that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue-based products are manufactured in a manner designed to prevent the introduction, transmission, and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing.

Submission and Filing of NDAs and BLAs

If clinical trials are successful, the next step in the development process is the preparation and submission to the FDA of a marketing application. The application is the vehicle through which sponsors formally propose that the FDA approve a new drug or biologic for marketing and sale in the United States for one or more indications. The application must contain a description of the manufacturing process and quality control methods, as well as results of all preclinical studies, toxicology studies and clinical trials, including negative or ambiguous results as well as positive findings, and proposed labeling, among other things. Every new product candidate must be the subject of an approved application before it may be commercialized in the United States. Under federal law, the submission of most applications is subject to an application user fee. Further, the sponsor of an approved application is also subject to an annual program fee. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

Following submission of an application, the FDA conducts a preliminary review of the application within 60 calendar days of its receipt and must inform the sponsor by that time or before whether the application is sufficiently complete to permit substantive review. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File determination to the sponsor. The FDA may request additional information and studies, and the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

Once the NDA or BLA is accepted for filing, the FDA sets a user fee goal date that informs the sponsor of the specific date by which the FDA intends to complete its review. The fee required for the submission and review of an application under the Prescription Drug User Fee Act, or PDUFA, is substantial (for example, for fiscal year 2023 this application fee is approximately $3.25 million), and the sponsor of an approved application is also subject to an annual program fee, currently more than $394,000 per eligible prescription product. Under the PDUFA, the FDA has agreed to specified performance goals in the review process of applications. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. For applications seeking approval of drugs that are not NMEs, the ten-month and six-month review periods run from the date that FDA receives the application. The review process and the PDUFA goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission. The FDA does not always meet its PDUFA goal dates for standard or priority NDAs or BLAs, and the review process is often extended by FDA requests for additional information or clarification. The FDA reviews NDAs and BLAs to determine, among other things, whether the proposed product candidate is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMPs to assure and preserve the product's identity, strength, quality and purity.

In connection with its review of an application, the FDA typically will inspect the facility or facilities where the product candidate is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in full compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The PHSA emphasizes the importance of manufacturing control for products like biologics whose attributes cannot be precisely defined. Additionally, before approving an application, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. With passage of the FDORA, Congress clarified the FDA's authority to conduct inspections by expressly permitting inspection of facilities involved in the preparation, conduct, or analysis of clinical and non-clinical studies submitted to the FDA as well as other persons holding study records or involved in the study process.

The FDA is also required to refer an application for a novel product candidate to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

The FDA's Decision on an Application

Under the PHSA, the FDA may approve a BLA if it determines that the product is safe, pure, and potent, and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure, and potent. The FDA may approve an NDA for a drug product if it determines that the product is safe and effective for its proposed use. In each case, the FDA must determine that the expected benefits of the proposed product outweigh its potential risks to patients. This "benefit-risk" assessment is informed by the extensive body of evidence about the product's safety and efficacy in the BLA or NDA. On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of clinical trial sites to assure compliance with GCPs, the FDA may issue an approval letter or a complete response letter.

If the application is not approved, the FDA will issue a complete response letter, which will contain details of the deficiencies in the submission and the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a complete response letter may submit to the FDA information that represents a complete response to the issues identified by the FDA, withdraw the application or request a hearing. Such resubmissions are classified under PDUFA as either Class 1 or Class 2. The classification of a resubmission is based on the information submitted by a sponsor in response to an action letter. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has two months to review a Class 1 resubmission and six months to review a Class 2 resubmission. The FDA will not approve an application until issues identified in the complete response letter have been addressed. If a complete response letter is issued, the sponsor will have

one year to respond to the deficiencies identified by the FDA, at which time the FDA can deem the application withdrawn or, in its discretion, grant the sponsor an additional six month extension to respond.

An approval letter, on the other hand, authorizes commercial marketing of the product with specific prescribing information for specific indications. The FDA may limit the approved indication(s) for use of the product. It may also require that contraindications, warnings, or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's efficacy and/or safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patent registries. If the FDA concludes a REMS is needed, the sponsor must submit a proposed REMS, and the FDA will not approve the NDA or BLA without an approved REMS, if required. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast Track, Breakthrough Therapy, Priority Review, and Regenerative Medicine Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited review if they demonstrate the potential to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, priority review designation, and regenerative medicine advanced therapy designation. The purpose of these programs is to provide important new drugs to patients earlier than under standard review procedures. None of these expedited programs change the standards for approval but each may help expedite the development or approval process governing product candidates.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy of safety factors. For fast track products, sponsors may have a higher number of interactions with the FDA during preclinical and clinical development and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees upon submission of the first section of the NDA or BLA. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

In addition, a new drug or biological product candidate may be eligible for breakthrough therapy designation if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

With passage of the 21st Century Cures Act in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative medicine advanced therapies, or RMAT. An RMAT is defined as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. In a recent guidance on expedited programs for regenerative medicine therapies for serious conditions, FDA specified that its interpretation of the definition of regenerative medicine advanced therapy products includes gene therapies that lead to a sustained effect on cells or tissues, such as in vivo AAV vectors delivered to non-dividing cells. The benefits of an RMAT designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review, and accelerated approval based on surrogate or intermediate endpoints.

Any product submitted to the FDA for approval, including a product with fast track, breakthrough, or RMAT designation, may also be eligible for priority review. A product is eligible for priority review if it is a product that is intended to treat a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months of the 60-day filing date.

Rare Pediatric Disease Designation and Priority Review Vouchers

In 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act requiring the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This program is designed to encourage development of new drug and biological products for prevention and treatment of "rare pediatric diseases" by, upon initial approval of an application meeting certain specified criteria, providing companies with a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease product receiving a priority review voucher may sell or otherwise transfer the voucher to another company. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted an application relying on the priority review voucher. The FDA may also revoke any priority review voucher if the rare pediatric disease product for which the voucher was awarded is not marketed in the United States within one year following the date of approval.

In order to receive a priority review voucher upon BLA or NDA approval, the product must receive designation from the FDA as a product for a rare pediatric disease prior to submission of the marketing application. A "rare pediatric disease" is a disease that is serious or life-threatening, in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years and affects fewer than 200,000 people in the United States, or affects more than 200,000 people in the United States but there is no reasonable expectation that the cost of developing and making available in the United States a product for such disease or condition will be recovered from sales in the United States of such product. In addition to receiving rare pediatric disease designation, in order to receive a priority review voucher, the NDA or BLA must be given priority review, rely on clinical data derived from studies examining a pediatric population and dosages of the product intended for that population, not seek approval for a different adult indication in the original rare pediatric disease product application and be for a product that does not include a previously approved active ingredient.

The Rare Pediatric Disease Priority Review Voucher Program was scheduled to expire after September 30, 2020. After that, only drugs designated as rare pediatric treatments and approved by the FDA by October 1, 2022, could receive a voucher. In December 2020, however, Congress renewed the program as part of the 2021 Coronavirus Response and Relief Supplemental Consolidated Appropriations Act through the federal fiscal year 2024. Thus, under the current statutory sunset provisions, the FDA may only award priority review vouchers for approved rare pediatric disease product applications if sponsors have rare pediatric disease designation for the drug granted by September 30, 2024. The FDA may not award any rare pediatric disease priority review vouchers after September 30, 2026.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA have imposed as part of the approval process. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money, and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that 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 lot release, the manufacturer

must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency, and effectiveness of pharmaceutical products. Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of HHS as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. In September 2021, the FDA published final regulations which describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. Moreover, with passage of the Pre-Approval Information Exchange Act in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. Previously, such communications were permitted under FDA guidance, but the new legislation explicitly provides protection to sponsors who convey certain information about products in development to payors, including unapproved uses of approved products.

In addition, the distribution of prescription drug products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Orphan Drug Designation and Exclusivity

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for rare diseases or conditions. In the United States, a rare disease or condition is statutorily defined under the Orphan Drug Act as a condition that affects fewer than 200,000 individuals in the United States or that affects more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a product for this type of disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation qualifies a company for tax credits and market exclusivity for seven years following the date of the product's marketing approval if granted by the FDA. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. A product becomes an orphan when it receives orphan drug designation from the Office of Orphan Products Development at the FDA based on acceptable confidential requests made under the regulatory provisions. The product must then go through the review and approval process like any other product.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first drug. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation before submitting an NDA or BLA.

If a product with orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same product for the same indication for seven years, except in certain 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 issued final guidance in September 2021 suggesting that it would not consider two gene therapy products to be different drugs solely based on minor differences in the transgenes or vectors. The FDA also intends to consider whether additional features of the final gene therapy product, such as regulatory elements and the cell type that is transduced (for genetically modified cells), should also be considered to be principal molecular structural features.

The period of market exclusivity begins on the date that the marketing application is approved by the FDA. If a product designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Further, orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan drug exclusivity regardless of a showing of clinical superiority. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drug products that received orphan drug designation before enactment of amendments to the FDCA in 2017 but have not yet been approved by FDA.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of regulatory exclusivity. For drug products, the six-month exclusivity may be attached to the term of any existing patent or regulatory exclusivity. For biologic products, the six-month period may be attached to any existing regulatory exclusivities but not to any patent terms. This six-month exclusivity may be granted if a sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity that cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, a sponsor must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are "abbreviated" because they generally do

not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug..." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety, which is the molecule or ion responsible for the action of the drug substance, that has previously been approved by the FDA in any other NDA. This interpretation of the FDCA by the FDA was confirmed with enactment of the Ensuring Innovation Act in April 2021. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the sponsor may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the sponsor and are essential to the approval of the application.

Section 505(b)(2) NDAs

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA pursuant to an NDA, a sponsor may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA that contains full reports of investigations of safety and effectiveness, but where at least some of the information required for approval comes from studies not conducted by, or for, the sponsor and for which the sponsor has not obtained a right of reference or use from the person by or for whom the investigations were conducted. This type of application permits reliance for such approvals on literature or on FDA's previous findings of safety and/or effectiveness for an approved drug product, and may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the previously approved reference listed drug, or RLD. The FDA may then approve the new product candidate for all, or some, of the label indications for which the RLD has been approved, as well as for any new indication sought by the 505(b)(2) sponsor.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the sponsor's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When a 505(b)(2) sponsor files its application with the FDA, the sponsor is required to certify to the FDA concerning any patents listed for the RLD in the Orange Book, except for patents covering methods of use for which the sponsor is not seeking approval. To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book.

Specifically, the sponsor must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved RLD's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the sponsor does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the sponsor is not seeking approval).

If the 505(b)(2) sponsor has provided a Paragraph IV certification to the FDA, the sponsor must also send notice of the Paragraph IV certification to the NDA and patent holders once the 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the 505(b)(2) application until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the sponsor. The 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired.

To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) sponsor.

Biosimilars and Exclusivity

The 2010 Patient Protection and Affordable Care Act included a subtitle called the Biologics Price Competition and Innovation Act, or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. A biosimilar is a biological product that is highly similar to an existing FDA-licensed "reference product." To date, the FDA has approved a number of biosimilars and the first interchangeable biosimilar product was approved on July 30, 2021, and a second product previously approved as a biosimilar was designated as interchangeable in October 2021. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars in the United States.

Under the BPCIA, a manufacturer may submit an application for licensure of a biological product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and the proposed biosimilar product in terms of safety, purity, and potency as shown through analytical studies, animal studies, and a clinical study or studies. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product in any given patient, and for products administered multiple times to an individual, that the biologic and the reference product may be altered or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. In December 2022, Congress clarified through the FDORA that the FDA may approve multiple first interchangeable biosimilar biological products so long as the products are all approved on the first day on which such a product is approved as interchangeable with the reference product.

Under the BPCIA, a reference biological product is granted 12 years of data exclusivity from the time of first approval of the product, and an application for a biosimilar product may not be submitted to the FDA until four years following the date of the initial approval of the reference product.

Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity, and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. There have been recent government proposals to reduce the 12-year reference product exclusivity period, but none has been enacted to date. At the same time, since passage of the BPCIA, many states have passed laws or amendments to laws, which address pharmacy practices involving biosimilar products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law. Since the passage of the BPCIA, many states have passed laws or amendments to laws, including laws governing pharmacy practices, which are state regulated, to regulate the use of biosimilars.

Patent Term Restoration and Extension

A patent claiming a new product or its method of use may be eligible for a limited patent term extension, also known as patent term restoration, under the Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. Patent term extension is generally available only for products whose active ingredient has not previously been approved by the FDA. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term extension cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension in consultation with the FDA.

FDA Approval of Companion Diagnostics

In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and in vitro companion diagnostics. According to the guidance, for novel drugs, a companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product's labeling. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. In July 2016, the FDA issued a draft guidance intended to assist sponsors of the drug therapeutic and in vitro companion diagnostic device on issues related to co-development of the products.

The 2014 guidance also explains that a companion diagnostic device used to make treatment decisions in clinical trials of a biologic product candidate generally will be considered an investigational device, unless it is employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, the diagnostic device generally will be considered a significant risk device under the FDA's Investigational Device Exemption, or IDE, regulations. Thus, the sponsor of the diagnostic device will be required to comply with the IDE regulations. According to the guidance, if a diagnostic device and a product are to be studied together to support their respective approvals, both products can be studied in the same investigational study, if the study meets both the requirements of the IDE regulations and the IND regulations. The guidance provides that depending on the details of the study plan and subjects, a sponsor may seek to submit an IND application alone, or both an IND- and IDE-application.

In April 2020, the FDA issued additional guidance which describes considerations for the development and labeling of companion diagnostic devices to support the indicated uses of multiple drug or biological oncology products, when appropriate. This guidance builds upon existing policy regarding the labeling of companion diagnostics. In its 2014 guidance, the FDA stated that if evidence is sufficient to conclude that the companion diagnostic is appropriate for use with a specific group of therapeutic products, the companion diagnostic's intended use/indications for use should name the specific group of therapeutic products, rather than specific products. The 2020 guidance expands on the policy statement in the 2014 guidance by recommending that companion diagnostic developers consider a number of factors when determining whether their test could be developed, or the labeling for approved companion diagnostics could be revised through a supplement, to support a broader labeling claim such as use with a specific group of oncology therapeutic products (rather than listing an individual therapeutic product(s)).

Under the FDCA, in vitro diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution.

The FDA previously has required in vitro companion diagnostics intended to select the patients who will respond to the product candidate to obtain premarket approval, or PMA, simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the sponsor must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee.

Federal and State Data Privacy and Security Laws

Under the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, the HHS has issued regulations to protect the privacy and security of protected health information, or PHI, used or disclosed by covered entities, including certain healthcare providers, health plans, and healthcare clearinghouses. HIPAA also regulates standardization of data content, codes, and formats used in healthcare transactions and standardization of identifiers for health plans and providers. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their regulations, including the omnibus final rule published on January 25, 2013, also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that are applicable to our business. In addition to possible federal civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. Accordingly, state attorneys general (along with private plaintiffs) have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. New laws and regulations governing privacy and security may be adopted in the future as well.

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020 and requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. The CCPA could impact our business activities depending on how it is interpreted and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional "GDPR-like" provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency, the California Privacy Protection Agency, whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah and Connecticut already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our current or future business activities, including certain clinical research, sales, and marketing practices and the provision of certain items and services to our customers, could be subject to challenge under one or more of such privacy and data security laws. The heightening compliance environment and the need to build and maintain robust and secure systems to comply with different privacy compliance and/or reporting requirements in multiple jurisdictions could increase the possibility that a healthcare company may fail to comply fully with one or more of these requirements. If our operations are found to be in violation of any of the privacy or data security laws or regulations described above that are applicable to us, or any other laws that apply to us, we may be subject to penalties, including potentially significant criminal, civil, and administrative penalties, damages, fines, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements, and/or oversight if we become subject to a consent decree or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our product candidates, once approved, are sold in a foreign country, we may be subject to similar foreign laws.

Regulation and Procedures Governing Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety, and efficacy, and governing, among other things, clinical trials, marketing authorization, commercial sales, and distribution of products. Whether or not it obtains FDA approval for a product, a sponsor will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically,

the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

On January 31, 2022, the new Clinical Trials Regulation (EU) No 536/2014 became effective in the European Union and replaced the prior Clinical Trials Directive 2001/20/EC. The new regulation aims at simplifying and streamlining the authorization, conduct and transparency of clinical trials in the European Union. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial to be conducted in more than one Member State of the European Union will only be required to submit a single application for approval. The submission will be made through the Clinical Trials Information System, a new clinical trials portal overseen by the European Medicines Agency, or the EMA, and available to clinical trial sponsors, competent authorities of the European Union Member States and the public.

The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the "EU Portal and Database"; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting European Union Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all European Union Member States in which an application for authorization of a clinical trial has been submitted, or concerned member states. Part II is assessed separately by each concerned European Union Member State. Strict deadlines have been established for the assessment of CTAs. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned European Union Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

The new regulation did not change the preexisting requirement that a sponsor must obtain prior approval from the competent national authority of the European Union Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different European Union Member States, the competent authorities in each of these European Union Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific study site after the applicable ethics committee has issued a favorable opinion.

Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the European Union at the EudraCT website: https://eudract.ema.europa.eu.

PRIME Designation in the European Union

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority Medicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies, or CAT, are appointed early in the PRIME scheme facilitating increased understanding of the product at the EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain a marketing authorization for a product under the European Union regulatory system, a sponsor must submit an MAA, either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in European Union Member States (decentralized procedure, national procedure, or mutual recognition procedure). A marketing authorization may be granted only to a sponsor established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, a sponsor must demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the

pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. Manufacturers must demonstrate the quality, safety, and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Specifically, the grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC lays down specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety, and efficacy of their products to EMA which provides an opinion regarding the application for marketing authorization. The European Commission grants or refuses marketing authorization in light of the opinion delivered by EMA.

Under the centralized procedure, the CHMP established at the EMA is responsible for conducting an initial assessment of a product. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated evaluation may be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation. If the CHMP accepts such a request, the time limit of 210 days will be reduced to 150 days, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that it is no longer appropriate to conduct an accelerated assessment.

Specialized Procedures for Gene Therapies

The EMA's CAT is responsible for assessing the quality, safety and efficacy of advanced-therapy medicinal products. Advanced-therapy medical products include gene therapy medicine, somatic cell therapy medicines and tissue-engineered medicines. The role of the CAT is to prepare a draft opinion on an application for marketing authorization for a gene therapy medicinal candidate that is submitted to the EMA. In the European Union, the development and evaluation of a gene therapy medicinal product must be considered in the context of the relevant European Union guidelines. The EMA may issue new guidelines concerning the development and marketing authorization for somatic cell therapy medicinal products and require that we comply with these new guidelines. Similarly, complex regulatory environments exist in other jurisdictions in which we might consider seeking regulatory approvals for our product candidates, further complicating the regulatory landscape. As a result, the procedures and standards applied to gene therapy products and cell therapy products may be applied to any of our gene therapy or genome editing product candidates, but that remains uncertain at this point.

The grant of marketing authorization in the European Union for gene therapy products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC includes specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety, and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Regulatory Data Protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if,

during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Patent Term Extensions in the European Union and Other Jurisdictions

The European Union also provides for patent term extension through Supplementary Protection Certificates, or SPCs. The rules and requirements for obtaining a SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained, which is described in detail below. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union.

Periods of Authorization and Renewals

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To that end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any authorization that is not followed by the placement of the drug on the European Union market (in the case of the centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid.

Regulatory Requirements after Marketing Authorization

Following approval, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product. These include compliance with the European Union's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. In addition, the manufacturing of authorized products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the EMA's cGMP requirements and comparable requirements of other regulatory bodies in the European Union, which mandate the methods, facilities, and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. Finally, the marketing and promotion of authorized products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the European Union under Directive 2001/83EC, as amended.

Orphan Drug Designation and Exclusivity

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the drug in the European Union would generate sufficient return to justify the necessary investment. For either of these conditions, the sponsor must demonstrate that there exists no satisfactory method of diagnosis, prevention, or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the drug will be of significant benefit to those affected by that condition.

An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized European Union marketing authorization. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, neither the EMA nor the European Commission or the member states can accept an application or grant a marketing authorization for a "similar medicinal product." A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may, however, be reduced to six years if, at the end of the

fifth year, it is established that the product no longer meets the criteria for orphan drug designation because, for example, the product is sufficiently profitable not to justify market exclusivity.

Approval of Companion Diagnostic Devices

In the European Union, medical devices such as companion diagnostics must comply with the General Safety and Performance Requirements, or SPRs, detailed in Annex I of the European Union Medical Devices Regulation (Regulation (EU) 2017/745), or MDR which came into force on May 26, 2021, and replaced the previously applicable EU Medical Devices Directive (Council Directive 93/42/EEC). Compliance with SPRs and additional requirements applicable to companion medical devices is a prerequisite to be able to affix the CE Mark of Conformity to medical devices, without which they cannot be marketed or sold. To demonstrate compliance with the SPRs, a manufacturer must undergo a conformity assessment procedure, which varies according to the type of medical device and its classification. The MDR is meant to establish a uniform, transparent, predictable, and sustainable regulatory framework across the European Union for medical devices.

Separately, the regulatory authorities in the European Union also adopted a new In Vitro Diagnostic Regulation (EU) 2017/746, which became effective in May 2022. The new regulation will replace the In Vitro Diagnostics Directive (IVDD) 98/79/EC. Manufacturers wishing to apply to a notified body for a conformity assessment of their in vitro diagnostic medical device had until May 2022 to update their Technical Documentation to meet the requirements and comply with the new, more stringent regulation. The regulation will, among other things: strengthen the rules on placing devices on the market and reinforce surveillance once they are available; establish explicit provisions on manufacturers' responsibilities for the follow-up of the quality, performance, and safety of devices placed on the market; improve the traceability of medical devices throughout the supply chain to the end-user or patient through a unique identification number; set up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the European Union; and strengthen rules for the assessment of certain high-risk devices, such as implants, which may have to undergo an additional check by experts before they are placed on the market.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom's withdrawal from the European Union took place on January 31, 2020. The European Union and the United Kingdom reached an agreement on their new partnership in the Trade and Cooperation Agreement, which was applied provisionally beginning on January 1, 2021, and which entered into force on May 1, 2021. The Trade and Cooperation Agreement focuses primarily on free trade by ensuring no tariffs or quotas on trade in goods, including healthcare products such as medicinal products. Thereafter, the European Union and the United Kingdom. will form two separate markets governed by two distinct regulatory and legal regimes. As such, the Trade and Cooperation Agreement seeks to minimize barriers to trade in goods while accepting that border checks will become inevitable as a consequence that the United Kingdom is no longer part of the single market. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising of England, Scotland and Wales, under domestic law whereas Northern Ireland continues to be subject to European Union rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law the body of European Union law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union.

Since a significant proportion of the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom. For example, the United Kingdom is no longer covered by the centralized procedures for obtaining European Union-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in the United Kingdom. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the European Union General Data Protection Regulation, or GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the EEA to the United Kingdom will remain lawful under GDPR. The Trade and Cooperation Agreement extended the application of the GDPR in the United Kingdom until the earlier of (1) the date on which adequacy decisions in relation to the United Kingdom are adopted by the European Commission under Article 36(3) of Directive (EU) 2016/680 and under Article 45(3) of Regulation (EU) 2016/679 or (2)

April 30, 2021 (which may be extended to June 30, 2021 unless either the European Union or the United Kingdom objects). The Trade and Cooperation Agreement also includes provisions that may end such period if the United Kingdom makes changes to its data protection legal framework, unless the European Union agrees upon such change. After such period, the United Kingdom will be a "third country" under the GDPR. We may incur liabilities, expenses, costs and other operational losses under GDPR and applicable European Union Member States and the United Kingdom privacy laws in connection with any measures we take to comply with them.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. 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 the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Additionally, in October 2022, President Biden signed an executive order to implement the European Union-U.S. Data Privacy Framework, which would serve as a replacement to the European Union-U.S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the European Union-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the European Union.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any product candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of such product candidates. Even if any product candidates we may develop are approved, sales of such product candidates will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers, and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such product candidates. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. 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 approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost- effective. A decision by a third-party payor not to cover any product candidates we may develop could reduce physician utilization of such product candidates once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, 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 and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. In addition, any companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement applicable to pharmaceutical or biological products will apply to any companion diagnostics.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of pharmaceuticals have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement, and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. 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 a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for any product candidates we may develop will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost-effectiveness of any product candidates we may develop to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies (so called health technology assessments) in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a product, or they may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on healthcare costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic, and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare Law and Regulation

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, 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, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious, or fraudulent or knowingly making, using, or causing to be made or used a false record or statement to avoid, decrease, or conceal an obligation to pay money to the federal government;
- the federal civil monetary penalty and false statement laws and regulations relating to pricing and submission of pricing information for government programs, including penalties for knowingly and intentionally overcharging 340b eligible entities and the submission of false or fraudulent pricing information to government entities;

- HIPAA, which created additional federal criminal laws that prohibit, 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 HITECH, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, on certain covered healthcare providers, health plans, and healthcare clearinghouses, as well as their respective business associates that perform services for them, that involve the use, or disclosure of, individually identifiable health information, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the Foreign Corrupt Practices Act, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, or PPACA, as amended by the Health Care Education Reconciliation Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the HHS, information related to payments and other transfers of value made by that entity to physicians, other healthcare providers and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are 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 in addition to requiring pharmaceutical manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures. In addition, certain state and local laws require drug manufacturers to register pharmaceutical sales representatives. 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.

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, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, integrity oversight, and reporting obligations, and the curtailment or restructuring of our operations.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the PPACA, which, among other things, includes changes to the coverage and payment for products under government healthcare programs. Among the provisions of the PPACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government

healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- an expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price" for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;
- an expansion of the types of entities eligible for the 340B drug discount program;
- establishment of the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable products to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient products to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- establishment of the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription product spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the United States since the PPACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2031 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. These Medicare sequester reductions have been suspended through the end of March 2022. From April 2022 through June 2022 a 1% sequester cut will be in effect, with the full 2% cut resuming thereafter. The American Taxpayer Relief Act of 2012, which was enacted in January 2013, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers, and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or TCJA, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseverable feature of the PPACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the PPACA are invalid as well. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden revoked those orders and issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under

Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2026 by the Infrastructure Investment and Jobs Act.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated “maximum fair price” under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. A number of states, for example, require drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers, wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional health care organizations and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. 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, which could result in reduced demand for our product candidates or additional pricing pressures.

There have been, and likely will continue to be, additional legislative and regulatory proposals at the foreign, federal, and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and develop product candidates.

Human Capital Resources

Employees

As of March 1, 2023, we had 68 full-time employees, including a total of 29 employees with M.D., Pharm.D. or Ph.D. degrees. Of these full-time employees, 48 employees are engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Diversity and Inclusion

We are committed to creating and maintaining a workplace free from discrimination or harassment on the basis of color, race, sex, national origin, ethnicity, religion, age, disability, sexual orientation, gender identification or expression, or any other status protected by applicable law. All of our employees must adhere to a code of conduct that sets standards for appropriate behavior. We believe that we will Succeed Through Diversity (one of our core values). We are committed to building a diverse employee population to enhance our ability to advance new drugs and benefit from our employees' broad range of experiences. At our company, compensation and advancement are based on qualifications, performance, skills and experience without regard to gender, race and ethnicity or any other status protected by applicable law.

Competitive Pay and Benefits

We strive to provide pay, comprehensive benefits, and services that help meet the varying needs of our employees. Our total rewards package includes competitive pay; comprehensive healthcare benefits package for employees, with family member healthcare benefits covered at 90%; health reimbursement account and health savings account options with company contribution; commuter benefits; tuition reimbursement benefits; unlimited discretionary paid time off and paid holidays; full pay for 12 weeks of parental leave; family medical leave; and hybrid and flexible work schedules. In addition, we offer every full-time employee, both exempt and non-exempt, the benefit of equity ownership in the company through stock options and other equity award grants. We also sponsor a 401(k) plan with a 4% match, with immediate vesting.

Employee Development and Training

We focus on attracting, retaining, and cultivating talented individuals. Employees are encouraged to attend scientific, clinical, and technological meetings and conferences and have access to broad resources they need to be successful. We actively work with managers to develop, create, and support individual development plans for our employees.

Safety

The safety, health, and wellness of our employees is a top priority. In response to the COVID-19 pandemic, we implemented safety protocols that are designed to comply with health and safety standards as required by federal, state, and local government agencies, taking into consideration guidelines of the Centers for Disease Control and Prevention and other public health authorities. Our protocols are updated in response to changes in those requirements and guidelines.

Our Corporate Information

We were incorporated under the laws of the state of Delaware under the name Hearing, Inc. in November 2013. We changed our name in April 2014. Our principal executive offices are located at 1325 Boylston Street, Suite 500, Boston, Massachusetts 02215, and our telephone number is (617) 370-8701. Our website address is www.decibeltx.com.

We own or have rights to trademarks, service marks and trade names that we use in connection with the operation of our business, including our corporate name, logos and website names. Other trademarks, service marks and trade names appearing in this Annual Report on Form 10-K are the property of their respective owners. Solely for convenience, some of the trademarks, service marks and trade names referred to in this Annual Report on Form 10-K are listed without the ® and ™ symbols, but we will assert, to the fullest extent under applicable law, our rights to our trademarks, service marks and trade names.

Available Information

We make available free of charge through our website our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons.

The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this Annual Report on Form 10-K by reference. We have included our website address in this Annual Report on Form 10-K as an inactive textual reference.

Item 1A. Risk Factors.

Our business is subject to a number of risks. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this Annual Report on Form 10-K, including the Management's Discussion and Analysis of Financial Condition and Results of Operations section and the consolidated financial statements and the related notes thereto in evaluating our company. The risks described below are not the only risks facing us. The occurrence of any of the following risks, or of additional risks and uncertainties not presently known to us or that we currently believe to be immaterial, could cause our business, prospects, results of operations and financial condition to suffer materially.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since our inception, have no products approved for sale and we expect to incur substantial losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred significant operating losses. Our net losses were $63.0 million and $51.8 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $277.5 million. To date, we have financed our operations primarily with proceeds from sales of preferred stock (including borrowings under convertible promissory notes, which converted into preferred stock in 2015), payments under the license and collaboration agreement, or the Regeneron Agreement, to which we are a party with Regeneron Pharmaceuticals, Inc., or Regeneron, from the sale of common stock in our initial public offering, or IPO and from the sale of common stock under our "at-the-market offering" program. Since inception, we have devoted substantially all of our resources on organizing and staffing, business planning, raising capital, establishing our intellectual property portfolio and performing research and development of our product candidates, programs and platform. We are still in the early stages of development of our product candidates, and we have not completed development of any product candidates. We expect to continue to incur significant expenses and operating losses over the next several years. Our operating expenses and net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses and capital expenditures will increase substantially if and as we:

- initiate and conduct our planned Phase 1/2 clinical trial of DB-OTO for the treatment of profound hearing loss caused by mutations of the OTOF gene;
- continue our current research programs and our preclinical development of AAV.103, AAV.104, AAV.105, our vestibular hair cell regeneration programs, our cochlear hair cell regeneration program and any product candidates that may arise from our current or future research programs;
- continue the clinical development of DB-020;
- advance additional product candidates into preclinical and clinical development;
- expand the capabilities of and invest in our platform;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- expand, maintain and protect our intellectual property portfolio;
- hire additional clinical, research, development, scientific, regulatory and quality control personnel;
- establish and maintain agreements with manufacturers for our product candidates; and
- add operational, legal, compliance, financial and management information systems and personnel, including personnel to support our research, product development and future commercialization efforts and support our operations as a public company.

In addition, we expect that our expenses will increase if, among other things:

- we are required by the U.S. Food and Drug Administration, or the FDA, the U.K. Medicines & Healthcare Products Regulatory Agency, or MHRA, the European Medicines Agency, or the EMA, or other regulatory authorities to perform trials or studies in addition to, or different than, those expected;
- there are any delays in completing our clinical trials or the development of any of our product candidates; or

- there are any third-party challenges to our intellectual property or we need to defend against any intellectual property-related claim.

We have no products for which we have obtained marketing approval and have not generated any revenue from product sales. Even if we obtain marketing approval of and are successful in commercializing one or more of our product candidates, we expect to incur substantial research and development and other expenditures to develop and market additional product candidates. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue.

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

We have never generated revenue from product sales and our most advanced product candidate is in early clinical trials. We expect that it will be many years, if ever, before we have a product candidate ready for commercialization. To become and remain profitable, we must succeed in developing, and eventually commercializing, a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, obtaining marketing approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain marketing approval. We are only in the preliminary stages of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately estimate or know the nature, timing or costs of the efforts that will be necessary to complete the preclinical and clinical development and commercialization of our product candidates or when, or if, we will be able to generate revenues or achieve profitability.

Our ability to generate revenue from product sales and achieve profitability depends on our ability to successfully develop and obtain the marketing approvals necessary to commercialize our product candidates. We do not have any products approved for sale and do not anticipate generating revenue from product sales for the next several years, if ever. Our ability to generate future revenue from product sales depends heavily on our success in:

- completing preclinical and clinical development of our product candidates in a timely manner and identifying and developing new product candidates;
- seeking and obtaining marketing approvals for any of our product candidates;
- commercializing product candidates for which we obtain marketing approval by establishing a sales force, marketing, medical affairs and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- achieving formulary status in hospitals and adequate coverage and reimbursement by government and third-party payors for our product candidates, if approved;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate products and services, in both amount and quality, to support development and market demand for our product candidates, if approved;
- obtaining market acceptance of our product candidates, if approved, as viable treatment options;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations in such collaborations;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- defending against third-party interference or infringement claims, if any; and
- attracting, hiring and retaining qualified personnel.

Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs in commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, MHRA, EMA or other regulatory agencies to perform clinical trials or studies in addition to those that

we currently anticipate. Even if we are able to generate revenue from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis as we expect to continue to engage in substantial research and development activities and to incur substantial expenses to develop and commercialize product candidates.

Our failure to become and remain profitable would depress our market value and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our research and development programs or commercialization efforts.

Since inception, we have used substantial amounts of cash. The development of biopharmaceutical product candidates is capital intensive and we expect that we will continue to expend substantial resources for the foreseeable future in connection with our ongoing activities. In particular, substantial resources will be required as we continue to conduct additional preclinical studies and prepare for and initiate our planned Phase 1/2 clinical trial of DB-OTO, advance our platform, continue research and development of AAV.103, AAV.104, AAV.105, our vestibular hair cell regeneration program, our cochlear hair cell regeneration program and any product candidates that may arise from our current or future research programs, and if and as we continue the clinical development of DB-020. Identifying potential product candidates, conducting preclinical testing and clinical trials and potentially submitting approvals of our product candidates is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. 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. Furthermore, we have incurred and expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital or obtain adequate funds when needed or on acceptable terms, we may be required to delay, limit, reduce or terminate our research and development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

We believe that our cash, cash equivalents and available-for-sale securities as of December 31, 2022 will enable us to fund our operating expenses and capital expenditure requirements into the first half of 2024. However, we have based this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of many 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 progress, costs and results of our planned Phase 1/2 clinical trial of DB-OTO and any future clinical development of DB-OTO;
- the approach we determine for the advancement of DB-020, including further potential clinical development;
- the scope, progress, costs and results of preclinical and clinical development for our other product candidates and programs, including AAV.103, AAV.104, AAV.105, our vestibular hair cell regeneration program and our cochlear hair cell regeneration program;
- the number of, and development requirements for, other product candidates that we may identify and develop;
- the scope, costs, timing and outcome of regulatory review of our product candidates;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the success of our collaboration with Regeneron;
- the payment or receipt of milestones and of other collaboration-based revenues, if any;
- our ability to establish and maintain additional strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;

- the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims;
- the extent to which we may acquire or in-license other products, product candidates and technologies;
- the impacts of the COVID-19 pandemic;
- the impact of continued increases in inflation rates or interest rates;
- the ability to receive additional non-dilutive funding, including grants from organizations and foundations; and
- the costs of operating as a public company.

Our independent registered public accounting firm has included an explanatory paragraph relating to our ability to continue as a going concern in its report on our audited financial statements included in this Annual Report on Form 10-K.

As a result of our recurring losses from operations and limited financial resources, there is substantial doubt about our ability to continue as a going concern. The report from our independent registered public accounting firm for the year ended December 31, 2022 includes an explanatory paragraph stating that our recurring losses and limited financial resources raise substantial doubt about our ability to continue as a going concern. If we seek additional financing to fund our business activities and there remains substantial doubt about our ability to continue as a going concern, investors or other financing sources may be unwilling to provide additional funding to us on commercially reasonable terms or at all. If we are unable to obtain sufficient funding, we could be forced to delay, reduce or eliminate all of our research and development programs or other business activities, and our financial condition and results of operations will be materially and adversely affected and we may be unable to continue as a going concern. In the future, reports from our independent registered public accounting firm may also contain statements expressing substantial doubt about our ability to continue as a going concern.

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 revenues from product sales, 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, other than the funds to which we are entitled under the Regeneron Agreement. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect their 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. Such restrictions could adversely impact our ability to conduct our operations and execute our business plan. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

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 or other arrangements 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.

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

We commenced operations in 2013, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, conducting research and development activities, identifying potential product candidates, soliciting input from regulators regarding development of these product candidates, securing intellectual property rights and undertaking preclinical studies and clinical trials. Other than DB-OTO, which received clearance from the FDA and authorization from the MHRA to initiate a Phase 1/2 clinical trial, all of our gene therapy product candidates are still in

the research or preclinical stage of development. We have not yet demonstrated our ability to successfully develop any product candidate, obtain marketing approvals, manufacture a commercial scale product, arrange for a third party to do so on our behalf, or conduct sales, marketing and distribution activities necessary for successful product commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing products.

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

We expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, stockholders should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

Our ability to use our NOLs and research and development tax credit carryforwards to offset future taxable income may be subject to certain limitations.

As of December 31, 2022, we had U.S. federal net operating loss carryforwards of approximately $217.9 million to offset future federal taxable income. Federal net operating losses, or NOLs, of $41.7 million will expire beginning in 2033. As of December 31, 2022, we had NOLs of $176.2 million which had an indefinite life. As of December 31, 2022, we had state net operating loss carryforwards of $210.5 million to offset future state taxable income, which will begin to expire in 2035. As of December 31, 2022, we had federal research and development tax credit carryforwards of $1.9 million, which expire beginning in 2033, state research and development tax credit carryforwards of $0.9 million, which expire beginning in 2032 and Orphan Drug credit carryforwards of $1.3 million, which expire beginning in 2043. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities.

We have a history of cumulative losses and anticipate that we will continue to incur significant losses in the foreseeable future; thus, we do not know whether or when we will generate taxable income necessary to utilize our NOLs or research and development tax credit carryforwards.

In general, under Section 382 of the Code and corresponding provisions of state law, a corporation that undergoes an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three-year period, is subject to limitations on its ability to utilize its pre-change NOLs and research and development tax credit carryforwards to offset future taxable income. We have not conducted a study to assess whether any such ownership changes have occurred. We may have experienced such ownership changes in the past and may experience such ownership changes in the future as a result of subsequent changes in our stock ownership (which may be outside our control). As a result, if, and to the extent that, we earn net taxable income, our ability to use our pre-change NOLs and research and development tax credit carryforwards to offset such taxable income may be subject to limitations. Our NOLs or credits may also be impaired under state law.

There is also a risk that due to regulatory changes, such as suspensions on the use of NOLs, or other unforeseen reasons, our existing NOLs could expire or otherwise become unavailable to offset future income tax liabilities. As described below in "Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition," the Tax Cuts and Jobs Act of 2017, or TCJA, includes changes to U.S. federal tax rates and the rules governing NOL carryforwards that may significantly impact our ability to utilize our NOLs to offset taxable income in the future. For these reasons, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes.

Risks Related to Discovery and Development

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

We are early in our development efforts. We have advanced only one product candidate, DB-020, into clinical trials, and it is still in early clinical trials. In addition, while DB-OTO has been cleared by the FDA and the MHRA to be evaluated in humans, we have not yet initiated a clinical trial of DB-OTO. Additionally, we have a portfolio of programs that are in preclinical development, and we may never advance another gene therapy product candidate 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, marketing approval and eventual commercialization of our product candidates, which may never

occur. We have not sought regulatory approval for DB-OTO or any other product candidate and do not expect to be in a position to do so for the foreseeable future. We currently generate no revenue from sales of any product, and we may never be able to develop or commercialize a marketable product.

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 IND-enabling studies;
- 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 FDA's Good Clinical Practices, or GCPs, Good Laboratory Practices, or GLPs, and any additional regulatory requirements from foreign regulatory authorities;
- 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 the FDA and other applicable regulatory authorities;
- establishment of arrangements for clinical supply and, where applicable, commercial manufacturing capabilities, including with third-party manufacturers;
- 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;
- procurement of intellectual property protection and regulatory exclusivity for our product candidates, and 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.

Many of these factors are beyond our control, including preclinical and clinical outcomes, the regulatory review process, potential threats to our intellectual property rights and the manufacturing, marketing, distribution and sales efforts of any collaborator. 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 develop and commercialize our product candidates, which would materially harm our business. If we are unable to advance our gene therapy 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. Our limited experience in conducting clinical development activities, including with respect to gene therapies, may adversely impact the likelihood that we will be successful in advancing our product candidates or programs.

We are heavily dependent on the success of our lead gene therapy product candidate, DB-OTO.

We currently have no products that are approved for commercial sale and may never be able to develop marketable products. We expect that a substantial portion of our efforts and expenditures for the foreseeable future will be devoted to DB-OTO. Accordingly, our business currently depends heavily on the successful development, regulatory approval and commercialization of DB-OTO. We cannot be certain that DB-OTO will receive regulatory approval or be successfully commercialized even if we receive regulatory approval. If we were required to discontinue development of DB-OTO, or if DB-OTO does not receive regulatory approval, fails to achieve significant market acceptance or fails to receive reimbursement, we would be delayed in our ability to achieve profitability, if ever.

Clinical development involves a lengthy and expensive process with uncertain outcomes, and results of earlier studies and trials may not be predictive of future clinical trial results. If our preclinical studies and clinical trials are not sufficient to

support regulatory approval of any of our product candidates, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development of such product candidate.

All of our product candidates are in preclinical development or early clinical trials and their risk of failure is high. Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any of our clinical trials will be conducted as planned or completed on schedule, or at all. A failure of one or more clinical trials can occur at any stage of testing, which may result from a multitude of factors, including, but not limited to, flaws in trial design, dose selection issues, participant enrollment criteria and failure to demonstrate favorable safety or efficacy traits.

Our preclinical programs are in the early stage, and we may not advance additional product candidates into clinical development when anticipated or at all. In addition, even if we identify a product candidate for a program, before we can commence clinical trials for such product candidate, we must complete extensive preclinical testing and studies that support our INDs and other regulatory filings in the United States and abroad. We cannot be certain of the timely completion or outcome of our preclinical testing and studies and cannot predict if regulatory authorities will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further advancement of any product candidates. We cannot be sure that we will be able to submit INDs, CTAs, or other regulatory filings for our preclinical product candidates on the timelines we expect, if at all, and we cannot be sure that submission of INDs will result in the FDA or other regulatory authorities allowing clinical trials to begin or to continue once commenced. Furthermore, product candidates are subject to continued preclinical safety studies and testing with respect to chemistry, manufacturing and controls data, which may be conducted concurrently with our clinical testing. The outcomes of these safety studies and other testing may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

The time required to obtain approval from the FDA, MHRA, EMA or other comparable foreign regulatory authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of regulatory authorities. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. We have not yet completed a clinical trial of any of our product candidates other than the Phase 1 clinical trial of DB-020 in healthy volunteers. Clinical trials may fail to demonstrate that our product candidates are safe for humans and effective for indicated uses. Even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application.

Furthermore, product candidates are subject to continued preclinical safety studies, which may be conducted concurrently with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

Other events that may prevent successful or timely completion of clinical development include:

- inability to generate sufficient preclinical, toxicology or other in vivo or in vitro data to support the initiation of clinical trials;
- delays in reaching a consensus with regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- delays related to COVID-19 disruptions at CROs, contract development and manufacturing organizations, or CDMOs, and/or clinical trial sites;
- delays in opening clinical trial sites or obtaining required institutional review board, or IRB, or institutional biosafety committee, or IBC, approval, or the equivalent review groups for sites outside the United States, at each clinical trial site;
- imposition of a clinical hold by regulatory authorities, including as a result of a serious adverse event or after an inspection of our clinical trial operations or trial sites;
- failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with GCPs;
- failure by investigators and clinical sites to adhere to protocols leading to variable results;
- failure of our delivery approach in humans;

- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions;
- failure of our third-party contractors to comply with regulatory requirements or to meet their contractual obligations to us in a timely manner, or at all;
- inability to enroll participants, delays in enrolling patients or delays in having enrolled participants complete their participation in a trial or return for post-administration follow-up;
- clinical trial sites or participants dropping out of a trial;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon development programs;
- occurrence of serious adverse events associated with the product candidate or administration of the product candidate that are viewed to outweigh its potential benefits;
- occurrence of serious adverse events or other unexpected events in trials of the same class of agents conducted by other sponsors;
- changes in regulatory requirements and guidance that require amending or submitting new clinical trial protocols;
- changes in the legal or regulatory regimes domestically or internationally related to patient rights and privacy; or
- lack of adequate funding to continue the clinical trial.

Any inability to successfully complete preclinical studies and clinical trials could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional preclinical studies or clinical trials to bridge our modified product candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

Gene therapy is an emerging field of drug development that poses many risks. We have only limited prior experience in gene therapy research and no prior experience in gene therapy clinical development. Our lack of experience and the limited patient populations for our gene therapy programs may limit our ability to be successful or may delay our development efforts.

Gene therapy is an emerging field of drug development with a limited number of gene therapies having received regulatory approval to date. Our gene therapy programs are at an early stage and there remain several areas of drug development risk, which pose particular uncertainty for our programs given the relatively limited development history of, and our limited prior experience with, gene therapies. Translational science, manufacturing materials and processes, safety concerns, regulatory pathway and clinical trial design and execution all pose particular risk to our drug development activities. Furthermore, the medical community's understanding of the genetic causes of many diseases continues to evolve and further research may change the medical community's views on what therapies and approaches are most effective for addressing certain diseases.

As an organization, we have not previously conducted any clinical trials of gene therapies. We have begun to establish our own gene therapy technical capabilities, but we will need to continue to expand those capabilities by either hiring internally or seeking assistance from outside service providers. Gene therapy is an area of significant investment by biotechnology and pharmaceutical companies and there may be a scarcity of talent available to us in these areas. If we are not able to expand our gene therapy capabilities, we may not be able to develop in the way we intend or desire any promising product candidates that emerge from our program or our other collaborative gene therapy sponsored research programs, which would limit our prospects for future growth. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of gene therapy product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trial or future clinical trials of gene therapy product candidates could prevent us from or delay us in commercializing our gene therapy product candidates.

As we prepare for the initiation of our first gene therapy clinical trial, we will need to build our internal and external capabilities in designing and executing a gene therapy clinical trial. There are many known and unknown risks involved in

translating preclinical development of gene therapies to clinical development, including selecting appropriate endpoints and dosage levels for dosing humans based on preclinical data. If we are unable to initiate and conduct our gene therapy clinical trials in a manner that satisfies our expectations or regulatory requirements, the value of our gene therapy programs may be diminished.

Our gene therapy product candidates and programs are based on a relatively novel technology, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all.

We are concentrating our therapeutic product research and development efforts primarily on our gene therapy programs. Our future success is almost entirely dependent on this therapeutic approach. Because our gene therapy product candidates are based on relatively novel technology, development problems we experience in the future related to our gene therapy platform may be difficult to solve and may cause delays and unanticipated costs. We may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial partners, which may prevent us from initiating or conducting clinical trials or commercializing our products on a timely or profitable basis, if at all.

Our gene therapy product candidates will need to meet purity, potency and safety standards applicable to any new biologic under the regulatory framework administered by the FDA. In addition to FDA oversight and oversight by IRBs, under guidelines promulgated by the U.S. National Institutes of Health, or NIH, gene therapy clinical trials may also be subject to review and oversight by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. Although the FDA decides whether individual gene therapy protocols may proceed, the review process and determinations of other reviewing bodies can impede or delay the initiation of a clinical trial, even if the FDA has reviewed the trial and approved its initiation.

In the European Union, the EMA's Committee for Advanced Therapies, or CAT, is responsible for assessing the quality, safety and efficacy of advanced-therapy medicinal products. Advanced-therapy medicinal products include gene therapy medicines, somatic-cell therapy medicines and tissue-engineered medicines. The role of the CAT is to prepare a draft opinion on an application for marketing authorization for a gene therapy medicinal candidate that is submitted to the EMA. In the European Union, the development and evaluation of a gene therapy product must be considered in the context of the relevant European Union guidelines. The EMA may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines. As a result, the procedures and standards applied to gene therapy products and cell therapy products may be applied to any gene therapy product candidate we may develop, but that remains uncertain at this point.

Adverse developments in preclinical studies or clinical trials of gene therapies conducted by others may cause the FDA, the EMA and other regulatory bodies to revise the requirements for approval of any gene therapy product candidates we may develop or limit the use of products utilizing gene regulation technologies, either of which could harm our business. The regulatory approval process for gene therapy product candidates such as ours can be more expensive and take longer than for other, better known, or more extensively studied pharmaceutical or other product candidates. Further, as we are developing novel potential treatments for diseases in which, in some cases, there is little clinical experience with potential new endpoints and methodologies, there is heightened risk that the FDA, the EMA or other 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. Any natural history studies that we may conduct or rely upon in our clinical development may not be accepted by the FDA, MHRA, EMA or other regulatory authorities. Regulatory agencies administering existing or future regulations or legislation may not allow production and marketing of gene therapy products in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays, or other impediments to our research programs or the commercialization of resulting products. Further, approvals by one regulatory agency may not be indicative of what other regulatory agencies may require for approval.

The regulatory review committees and advisory groups described above and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional preclinical studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these treatment candidates, or lead to significant post-approval limitations or restrictions. As we advance our research programs and develop future product candidates, we will be required to consult with these regulatory and advisory groups and to comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of any product candidates we identify and develop. 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. The first approvals of gene therapy products by the FDA only occurred in 2017. As a result, it is

difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union, or how long it will take to commercialize any product candidate that receives marketing approval.

The outcome of preclinical studies and earlier-stage clinical trials may not be predictive of future results or the success of later-stage clinical trials.

The results of preclinical studies may not be predictive of the results of clinical trials, and the results of any early-stage clinical trials may not be predictive of the results of the later-stage clinical trials or from clinical trials of the same product candidates in other indications. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. For example, the results of the Phase 1 clinical trial of DB-020 in healthy volunteers and the interim data from the Phase 1b clinical trial of DB-020 in patients undergoing treatment with cisplatin may not be indicative of the results of a later-stage clinical trial. In addition, if successful, the results of our planned Phase 1/2 clinical trial of DB-OTO may not be predictive of the results of further clinical trials of this product candidate or any other gene therapy product candidates. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. Our future clinical trials may not ultimately be successful or support further clinical development of any of our product candidates. There is a high failure rate for product candidates proceeding through clinical trials, and because our gene therapy product candidates are based on a relatively novel technology, the likelihood of success is harder to determine. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving encouraging results in earlier studies. Any such setbacks in our clinical development could materially harm our business, financial condition, results of operations and prospects.

Interim and preliminary results from our clinical trials that we announce or publish from time to time may change as more participant data become available and are subject to audit and verification procedures, which could result in material changes in the final data.

From time to time, we may publish interim or preliminary results from our clinical trials, such as the data from the interim analysis of our Phase 1b clinical trial of DB-020 that we announced in June 2022. Interim results from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as more participant data become available. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully evaluate all data. Preliminary or top-line results also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. Additionally, preliminary data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. As a result, interim and preliminary data should be viewed with caution until the final data are available. Differences between preliminary or interim data and final data could be material and could significantly harm our reputation and business prospects and may cause the trading price of our common stock to fluctuate significantly.

If we experience delays or difficulties in participant enrollment for clinical trials, our research and development efforts and the receipt of necessary regulatory approvals could be significantly delayed or prevented.

Identifying and qualifying individuals to participate in clinical trials is critical to our success. We may not be able to identify, recruit and enroll a sufficient number of participants, or those with required or desired characteristics, to complete our clinical trials in a timely manner. Any delay or difficulty in participant enrollment could significantly delay or otherwise hinder our research and development efforts and delay or prevent receipt of necessary regulatory approvals.

Participant enrollment and trial completion is affected by factors including:

- perceived risks and benefits in the case of our gene therapy product candidates, of a small virus commonly used in gene therapy, known as adeno-associated virus, or AAV, for the potential treatment of hearing loss and balance disorders;
- size of the patient population, including for rare diseases such as the rare diseases on which our gene therapy programs are currently focused, and process for identifying potential trial participants;
- the potential direct or indirect impact of the COVID-19 pandemic;
- design of the trial;

- inclusion and exclusion criteria;
- perceived risks and benefits of the product candidate;
- availability of competing therapies and clinical trials;
- severity of the disorder under investigation;
- availability of genetic testing for potential participants;
- proximity and availability of clinical trial sites for potential participants;
- ability to obtain and maintain informed consent;
- risk that enrolled participants will drop out before completion of the trial;
- the commitment of our clinical investigators to identify potential participants;
- patient referral practices of physicians;
- ability to monitor participants adequately during and after product candidate administration; and
- ability to recruit and retain trial participants due to other unforeseen circumstances.

For example, due to the continued impact of the COVID-19 pandemic on the pace of patient screening and enrollment and the closure of trial sites in the United States that we had expected to re-open, we experienced a delay in when we expected to report results from an interim analysis of our Phase 1b clinical trial of DB-020.

Our gene therapy programs are initially targeting orphan diseases with relatively small populations, which limits the pool of potential participants for our gene therapy clinical trials. Because gene therapy trials generally require participants who have not previously received any other gene therapy or potentially other pharmacological therapeutics for the same indication or treatment with medical devices (for example, cochlear implants), we will also need to compete with others who are also developing gene therapies or pharmacologic therapeutics for these same indications for the same group of potential clinical trial participants. This competition could reduce the number and types of potential participants available to us, as some potential participants who might have opted to enroll in our clinical trials may instead opt to enroll in one being conducted by one of our competitors. In addition, individuals may also be unwilling to participate in our clinical trials because of negative publicity from adverse events in the biotechnology or biopharmaceutical industries, particularly to the extent that such negative publicity is related to gene therapy. Challenges in recruiting and enrolling sufficient numbers of suitable participants in clinical trials could increase costs, affect the timing and outcome of our planned clinical trial or future clinical trials and result in delays to our current development plan for our product candidates. If we have difficulty enrolling a sufficient number of individuals to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would harm our business, financial condition, results of operations and prospects.

Our product candidates or the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.

We have only conducted a clinical trial of DB-020 and have not conducted clinical trials in any of our gene therapy programs.

In past clinical trials that were conducted by others with non-AAV vectors, several significant side effects were caused by gene therapy product candidates, including reported cases of leukemia and death. Other potential side effects associated with both AAV and non-AAV vectors could include immunologic reactions or insertional oncogenesis, which is the process whereby the insertion of a functional gene near a gene that is important in cell growth or division results in uncontrolled cell division, which could potentially enhance the risk of malignant transformation. If our gene therapy product candidates demonstrate a similar adverse effect, or other adverse events, we may be required to halt or delay further clinical development of our gene therapy product candidates.

In addition to side effects caused by the product candidate itself, the administration process also can cause side effects. Although the procedure we have developed to deliver our gene therapy product candidate is based on the surgical approach employed by neurotologists and pediatric otolaryngologists during a standard cochlear implantation procedure, any surgical procedure runs risks related to infection and damage to parts of the body adjacent to the treated area. In addition, until we are able to test the procedure on humans, we cannot be certain that our delivery mechanism will be successful. If side effects were to occur in connection with the surgical procedure during our planned clinical trials or if we fail to successfully apply our delivery approach in humans, our clinical trials could be suspended or terminated.

If, in the future, we are unable to demonstrate that trial side effects were not caused by our product candidates or the related procedures, the FDA, the MHRA, the EMA or other 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 any future serious adverse events are not product-related, and regulatory authorities do not order us to cease further development of our product candidates, such occurrences could cause our reputation to suffer and affect patient recruitment or the ability of enrolled participants to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any 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, results of operations and prospects significantly.

Regulatory approval of and/or demand for our potential products will depend in part on public acceptance of the use of gene therapies for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapies 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. In 1999, there was public backlash against the field of gene therapy following the death of a participant in a clinical trial, which utilized a different type of gene therapy product candidate vector, from an extreme type of immune response that can be life-threatening. Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and could significantly harm our business, financial condition, results of operations and prospects.

We may not be successful in our efforts to identify or discover additional potential product candidates.

A key element of our strategy is to apply our proprietary platform to expand our pipeline of gene therapies for the treatment of acquired hearing and balance disorders. The discovery activities that we are conducting may not be successful in identifying product candidates that are useful in restoring or improving hearing or balance. The process by which we identify product candidates may fail to yield product candidates for clinical development for a number of reasons, including those discussed in these risk factors and also:

- we may not be able to assemble sufficient resources to acquire or discover additional product candidates;
- competitors may develop alternatives that render our potential product candidates obsolete or less attractive;
- potential product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- potential product candidates may, on further study, be shown to have harmful side effects, toxicities or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance;
- potential product candidates may not be effective in treating their targeted disorders;
- the market for a potential product candidate may change so that the continued development of that product candidate is no longer reasonable;
- a potential product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; or
- the regulatory pathway for a potential product candidate may be too complex and difficult to navigate successfully or economically.

We may expend our limited resources to pursue a particular program, product candidate or indication and fail to capitalize on programs, 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 expect to focus on product candidates that we identify for specific indications among many potential options. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential, or we may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. Our resource allocation decisions may cause us to fail to 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 medicines. 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. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

Clinical trial and product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of our product candidates.

We face an inherent risk of clinical trial and product liability exposure related to the testing of product candidates in clinical trials, and we will face an even greater risk if we commercially sell any products that we may develop. While we currently have no products that have been approved for commercial sale, the current and future use of product candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies or others selling such products. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend any related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize our product candidates.

We will need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of any 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. If a successful clinical trial or product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

Risks Related to Manufacturing

The manufacture of gene therapy products is complex and difficult and is subject to a number of scientific and technical risks, some of which are common to the manufacture of drugs and biologics and others of which are unique to the manufacture of gene therapies. We could experience manufacturing problems that result in delays in our gene therapy development or commercialization programs.

Gene therapy drug products are complex and difficult to manufacture. For our IND-enabling studies of DB-OTO and our planned Phase 1/2 clinical trial of DB-OTO, we are relying on the manufacturing facility of Catalent Maryland, Inc., or Catalent, for supply of the product candidate. In addition to Catalent, we also rely upon other CROs and CDMOs for providing certain materials for the manufacturing process.

We believe that the high demand for clinical gene therapy material and a scarcity of potential contract manufacturers may cause long lead times for establishing manufacturing capabilities for gene therapy drug development activities. Even after a manufacturer is engaged, any problems that arise during manufacturing process development may result in unanticipated delays to our timelines, including delays attributable to securing additional manufacturing slots. There may also be long lead times to manufacture or procure starting materials such as plasmids and cell lines, especially for high-quality starting materials that are current good manufacturing process, or cGMP, compliant. In particular, plasmids, cell lines and other starting materials for gene therapy manufacture are usually sole sourced, as there are a limited number of qualified suppliers. The progress of our gene therapy programs is highly dependent on these suppliers providing us or our contract manufacturers with the necessary starting materials that meet our requirements in a timely manner. A failure to procure or a shortage of necessary starting materials likely would delay our manufacturing and development timelines.

Problems with the manufacturing process, including even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims and insufficient inventory. If we successfully develop product candidates, we may encounter problems achieving adequate quantities and

quality of clinical-grade materials that meet FDA or other applicable standards or specifications with consistent and acceptable production yields and costs.

A number of factors common to the manufacturing of biologics and small molecules could also cause production issues or interruptions for gene therapies, including raw material or starting material variability in terms of quality, cell line viability, productivity or stability issues, shortages of any kind, shipping, distribution, storage and supply chain failures, growth media contamination, equipment malfunctions, operator errors, facility contamination, labor problems, natural disasters, public health epidemics, disruption in utility services, terrorist activities or "acts of God" that are beyond our or our contract manufacturers' control. It is often the case that early-stage process development is conducted with materials that are not manufactured using cGMP starting materials, techniques or processes and which are not subject to the same level of analysis that would be required for clinical grade material. We may encounter difficulties in translating the manufacturing processes used to produce research grade materials to cGMP compliant processes, and any changes in the manufacturing process may affect the safety and efficacy profile of our product candidates.

In addition, the FDA and comparable regulatory authorities in other jurisdictions may require us to submit samples of any lot of any approved biological product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA or comparable regulatory authorities in other jurisdictions may prohibit the distribution of 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 and product recalls.

Given the nature of biologics manufacturing, there is a risk of contamination during manufacturing. Any contamination could materially harm our ability to produce product candidates on schedule and could harm our results of operations and cause reputational damage. Some of the raw materials that we anticipate will be required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of any product candidates we may develop could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially harm our development timelines and our business, financial condition, results of operations and prospects.

An important part of manufacturing drug products is performing analytical testing. Analytical testing of gene therapies involves tests that are more numerous, more complex in scope and take a longer time to develop and to conduct as compared to traditional drugs. We and our contract manufacturers need to expend considerable time and resources to develop assays and other analytical tests for our gene therapy product candidates, including assays to assess the titer and potency of our gene therapy product candidates. Some assays need to be outsourced to specialized testing laboratories. Even when assays are developed, they need to be further tested, qualified or validated depending on the nature of the assay and the stage of product candidate development, which may take substantial time and resources. Because of the lagging nature of analytical testing, we may proceed with additional manufacturing and other development activities without having first fully characterized our manufactured materials. If the results of the testing fail to meet our expectations, we may need to delay or repeat certain manufacturing and development activities.

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

We rely on third-party suppliers for manufacturing, testing and supply of certain materials and components required for the production of our product candidates. Our dependence on these third-party manufacturers and suppliers and the challenges we may face in obtaining adequate manufacturing, testing and 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 manufacturing and testing slots and for certain 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 other companies that are larger than we are. We cannot be certain that our manufacturers and suppliers will continue to provide us with the manufacturing slots and quantities of these raw materials that we require or satisfy our anticipated specifications and quality requirements. Any supply interruption in limited or sole sourced manufacturing or 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. In addition, any disruptions in the business operations of our manufacturers or suppliers could have a direct impact on the manufacturing of our product candidates. For example, one of our key suppliers recently announced facility consolidations and other cost-cutting measures requiring us to transfer certain of our DB-OTO manufacturing activities to another manufacturing site. Other third party gene therapy manufacturers that do not support our programs have taken similar cost-cutting measures in recent months. While these disruptions have not had a material impact on our business to date, any performance failure on the part of our manufacturers or suppliers or consolidations that hinder our ability to obtain necessary supplies to conduct our planned development activities 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 Our Dependence on Third Parties

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a new drug application, or NDA, or biologics license application, or BLA, on a timely basis and must adhere to the FDA's GLP and cGMP regulations enforced by the FDA through its facilities inspection program. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition, results of operations and prospects may be materially harmed.

Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in supply. An alternative manufacturer would need to be qualified through an NDA or BLA supplement, which could result in further delay. The regulatory agencies may also require additional studies or trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement

suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

We rely, and expect to continue to rely, on third parties to conduct, supervise and monitor our clinical trials, and if these third parties perform in an unsatisfactory manner, it may harm our business.

We rely, and expect to continue to rely, on CROs and clinical trial sites to ensure our clinical trials are conducted properly and on time and we expect to have limited influence over their actual performance. We control only certain aspects of our CROs' activities. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces these GCPs through periodic inspections of sponsors, principal investigators and clinical sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving any marketing applications. Upon inspection, the FDA may determine that our clinical trials did not comply with GCPs. In addition, our clinical trials will require a sufficient number of participants to evaluate the safety and effectiveness of our product candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of participants, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and 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 would be harmed, our costs could increase and our ability to generate revenues could be delayed.

The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, impose obligations on "covered entities," including certain healthcare providers, health plans and healthcare clearinghouses, as well as their respective "business associates" that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. Such obligations may require us to pass certain obligations on to our CROs or other third parties with whom we do business, including transferal of personal information or individually identifiable health information.

We depend on single-source suppliers for some of the components and materials used in our product candidates.

We depend on single-source suppliers for some of the components and materials used in our product candidates. We cannot ensure that these suppliers or service providers will remain in business, have sufficient capacity or supply to meet our needs or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of single-source suppliers of raw materials, components, key processes and finished goods exposes us to several risks, including disruptions in supply, price increases or late deliveries. There are, in general, relatively few alternative sources of supply for substitute components. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components, materials and processes could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any single-source supplier or service provider could lead to supply delays or interruptions, which would damage our business, financial condition, results of operations and prospects.

If we have to switch to a replacement supplier, the manufacture and delivery of any product candidates we may develop could be interrupted for an extended period, which could adversely affect our business. Establishing additional or replacement suppliers, if required, may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. While we seek to maintain adequate inventory of the single source components and materials used in our products, any interruption or delay in the supply of components or materials, or our inability to obtain components or

materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand for our product candidates.

We expect to depend on collaborations with third parties for the research, development, manufacture and commercialization of programs or product candidates. If these collaborations are not successful, our business could be adversely affected.

As part of our strategy, we intend to maximize the value of our pipeline and our platform by exploring strategic collaborations. If we enter into such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of any product candidates we develop or commercialize with them. Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. For instance, under the Regeneron Agreement, we are dependent on Regeneron to contribute various technologies, employees and research services.

Collaborations that we enter into may not be successful, and any success will depend heavily on the efforts and activities of our collaborators. For example, in September 2018, we entered into a collaboration and license agreement with Oricula Therapeutics, LLC, but in September 2019, we terminated the agreement. Collaborations pose a number of risks, including the following:

- collaborators have significant discretion in determining the amount and timing of efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development of our product candidates or may elect not to continue or renew programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may not pursue commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew commercialization programs based on results of clinical trials or other studies, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that may divert resources or create competing priorities;
- collaborators may delay programs, preclinical studies or clinical trials, provide insufficient funding for programs, preclinical studies or clinical trial programs, stop a preclinical study or 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;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our stockholders about the status of such product candidates on a discretionary basis;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates and products if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over intellectual property or proprietary rights, contract interpretation or the preferred course of development, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly obtain, maintain, enforce, defend or protect our intellectual property or proprietary rights or may use our proprietary information in such a way as to potentially lead to disputes or legal proceedings that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe, misappropriate or otherwise violate the intellectual property or proprietary rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. If any collaborations that we enter into do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of our collaborators.

Additionally, subject to its contractual obligations to us, if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

If conflicts arise between us and our current or future collaborators, these parties may act in a manner adverse to us and could limit our ability to implement our strategies.

If conflicts arise between us and Regeneron or any future collaborators, the other party may act in a manner adverse to us and could limit our ability to implement our strategies. Our collaborators may develop, either alone or with others, products in related fields that are competitive with our product candidates that are the subject of these collaborations with us. Competing products, either developed by the collaborators or to which the collaborators have rights, may result in the withdrawal of support for our product candidates.

Some of our future collaborators could also become our competitors. Our collaborators could develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain timely regulatory approvals, terminate their agreements with us prematurely, fail to devote sufficient resources to the development and commercialization of products, or merge with or be acquired by a third party who may do any of these things. Any of these factors could harm our product development efforts.

If we are not able to establish or maintain collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans and our business could be adversely affected.

We face significant competition in attracting appropriate collaborators, and a number of more established companies may also be pursuing strategies to license or acquire third-party intellectual property rights that we consider attractive. These established companies may have a competitive advantage over us due to their size, financial resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. 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, MHRA, EMA or other regulatory authorities, 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 products, 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, the terms of any existing collaboration agreements, and industry and market conditions generally. The collaborator may also have the opportunity to collaborate on other product candidates or technologies for similar indications and will have to evaluate whether such a collaboration could be more attractive than the one with us for our product candidate.

Collaborations are complex and time-consuming to negotiate, document and execute. In addition, consolidation among large pharmaceutical and biotechnology companies has reduced the number of potential future collaborators.

We may not be able to establish additional collaborations on a timely basis, on acceptable terms or at all, including for DB-020 for which we are considering a range of potential approaches for its further development and commercialization, including entering into a strategic collaboration. If we are unable to do so, we may have to curtail the development of DB-020 or such other product candidate, as the case may be, for which we are seeking to collaborate, reduce or delay its program or one or more of our other 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 fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our platform.

Risks Related to Commercialization

We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our product candidates from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of many of the disorders for which we are developing our product candidates. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

We expect to face competition from existing products and product candidates in development for each of our programs. There are currently no approved drugs for the treatment of hearing loss or balance disorders.

We expect that our product candidates and programs for congenital, monogenic hearing loss and for acquired hearing loss will compete with product candidates and programs being advanced by:

- Akouos, Inc., which is developing AK-OTOF, a gene therapy for profound hearing loss resulting from deficiency in OTOF, which is in clinical development, and has preclinical gene therapy programs targeting GJB2 and Usher Syndrome Type 3A and for treatment of sensorineural hearing loss through hair cell regeneration. Akouos, Inc. received clearance of its IND for AK-OTOF in September 2022. In December 2022, Eli Lilly and Company acquired Akouos, Inc.; and
- Sensorion SA, or Sensorion, which has three gene therapy programs targeting GJB2-mediated hearing loss, Usher Syndrome Type I and OTOF-deficiency in preclinical development. Sensorion has announced that it plans to submit a CTA within Europe for its OTOF-GT program in the first half of 2023.

We are aware of PEDMARK, a formulation of sodium thiosulfate delivered via systemic injection, developed by Fennec Pharmaceuticals, Inc. that in September 2022 received FDA approval for use to reduce the risk of ototoxicity associated with cisplatin in pediatric patients one month of age and older with localized, non-metastatic, solid tumors. We are also aware of product candidates in development, including SENS-401, a small molecule being developed by Sensorion that is in Phase 2 clinical trials for prevention of chemotherapy related hearing loss, D-methionine, an amino acid that has been shown to protect against hearing loss in experimental settings, and SPI-3005, an oral agent primarily being developed by Sound Pharmaceuticals, Inc. for noise and age-related hearing loss that is in Phase 2 clinical trials for chemotherapy related hearing loss. We are also aware of additional therapeutic approaches in preclinical development that may target prevention of hearing loss in patients receiving cisplatin chemotherapy. We are also aware that Sound Pharmaceuticals, Inc. is pursuing treatments for Meniere's Disease, a balance disorder.

Our commercial opportunity could be reduced or eliminated if our 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 our product candidates, or that would render any product candidates that we may develop obsolete or non-competitive. Our competitors also may obtain FDA or other regulatory approval for their product candidates more rapidly than we may obtain approval for ours, or may obtain regulatory exclusivity, any of which could result in our competitors establishing a strong

market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Furthermore, mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors.

The market opportunities for our product candidates may be smaller than we anticipated or may be limited to those patients who are ineligible for or have failed prior treatments. If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

Our current and future target patient populations are based on our beliefs and estimates regarding the incidence or prevalence of certain types of the indications that may be addressable by our product candidates, which is derived from a variety of sources, including scientific literature and surveys of clinics. Our projections may prove to be incorrect and the number of potential patients may turn out to be lower than expected. The total addressable market opportunity for our product candidates will ultimately depend upon a number of factors including the diagnosis and treatment criteria included in the final label, if approved for sale in specified indications, acceptance by the medical community, patient access and product pricing and reimbursement. Even if we obtain significant market share for our product candidates, because the potential target populations could be small, we may never achieve profitability without obtaining regulatory approval for additional indications.

Negative public opinion of gene therapy and increased regulatory scrutiny of gene therapy and genetic research may adversely impact the development or commercial success of our current and future product candidates.

Our potential therapeutic products involve introducing genetic material into a patient's cells. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene therapy and gene regulation for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy and gene regulation 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 in lieu of, or in addition to, existing treatments with which they are already familiar and for which greater clinical data may be available.

More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products once approved. For example, in 2003, trials using early versions of murine gamma-retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events, including reported cases of leukemia. Although none of our current product candidates utilizes murine gamma-retroviral vectors, our product candidates use AAV viral vectors. Among the risks in any gene therapy product based on viral vectors are the risks of immunogenicity, elevated liver enzymes and insertional oncogenesis. If any of our vectors demonstrate a similar effect, we may decide or be required to halt or delay further clinical development of any product candidates that utilize that vector. Adverse events in our or others' clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. The risk of cancer remains a concern for gene therapy and we cannot assure that it will not occur in any of our planned or future clinical trials or in any clinical trials conducted by other companies. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material.

Even if any product candidate we develop receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, patient advocacy groups, third-party payors and others in the medical community necessary for commercial success.

If any product candidate we develop receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, patient advocacy groups, third-party payors and others in the medical community. Sales of medical products depend in part on the willingness of physicians to prescribe the treatment, which is likely to be based on

a determination by these physicians that the products are safe, therapeutically effective and cost-effective. In addition, the inclusion or exclusion of products from treatment guidelines established by various physician groups and the viewpoints of influential physicians can affect the willingness of other physicians to prescribe the treatment. We cannot predict whether physicians, physicians' organizations, hospitals, other healthcare providers, government agencies or private insurers will determine that our product is safe, therapeutically effective and cost-effective as compared with competing treatments. Efforts to educate those in the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- the effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement, and patients' willingness to pay out of pocket for required co-payments or in the absence of third-party coverage or adequate reimbursement;
- the prevalence and severity of any side effects;
- publication of any post-approval data on the effectiveness and safety of the product; and
- any restrictions on the use of our products, if approved, together with other medications.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing our product candidates if and when they are approved.

We currently have no sales, marketing or commercial product distribution capabilities and have no experience in commercializing products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales, marketing and distribution organization, either ourselves or through collaborations or other arrangements with third parties.

In the future, we expect to build a sales and marketing infrastructure to market some of our product candidates. There are costs and risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. These efforts may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel. We must also compete with other biotechnology and biopharmaceutical companies to recruit, hire, train and retain marketing and sales personnel.

Factors that may inhibit our efforts to commercialize our products on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales, marketing, coverage or reimbursement, customer service, medical affairs and other support personnel;
- the inability of sales personnel to educate adequate numbers of physicians on the benefits of any future products;
- the inability of reimbursement professionals to negotiate arrangements for formulary access, reimbursement and other acceptance by payors;
- the inability to price our products at a sufficient price point to ensure an adequate and attractive level of profitability;
- restricted or closed distribution channels that make it difficult to distribute our products to segments of the patient population;

- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;
- unforeseen costs and expenses associated with creating an independent sales and marketing organization; and
- unforeseen issues impacting supply, distribution, sales and marketing.

If we are unable to establish our own sales, marketing and distribution capabilities and we enter into arrangements with third parties to perform these services, our product revenues and our profitability, if any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. There can be no assurance that we will be able to develop in-house sales, marketing and distribution capacities or establish or maintain relationships with third parties to perform these services. As a result, we may not successfully commercialize any product in any jurisdiction.

If any of our product candidates receives marketing approval and we, or others, later discover that the drug is less effective than previously believed or causes undesirable side effects that were not previously identified, our ability to market the drug could be compromised.

Clinical trials of our product candidates are conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If one or more of our product candidates receives regulatory approval, and we, or others, later discover that they are less effective or less durable than previously believed, or cause undesirable side effects, a number of potentially significant negative consequences could result, including:

- withdrawal or limitation by regulatory authorities of approvals of such product;
- seizure of the product by regulatory authorities;
- recall of the product;
- restrictions on the marketing of the product or the manufacturing process for any component thereof;
- requirement by regulatory authorities of additional warnings on the label, such as a “black box” warning or contraindication;
- requirement that we implement a Risk Evaluation and Mitigation Strategy, or REMS, or create a medication guide outlining the risks of such side effects for distribution to patients;
- commitment to expensive post-marketing studies as a prerequisite of approval by regulatory authorities of such product;
- the product may become less competitive;
- initiation of regulatory investigations and government enforcement actions;
- initiation of legal action against us to hold us liable for harm caused to patients; and
- harm to our reputation and resulting harm to physician or patient acceptance of our products.

Any of these events could prevent us from achieving or maintaining market acceptance of a particular product candidate, if approved, and could significantly harm our business, financial condition, and results of operations.

Our future growth depends, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties that, if they materialize, could harm our business.

Our future profitability will depend, in part, on our ability to commercialize our product candidates in markets outside of the United States. If we commercialize our product candidates in foreign markets, we will be subject to additional risks and uncertainties, including:

- economic weakness, including inflation, or political instability in particular economies and markets;

- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements, many of which vary between countries;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- tariffs and trade barriers, as well as other governmental controls and trade restrictions;
- other trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or foreign governments;
- longer accounts receivable collection times;
- longer lead times for shipping;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is common;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- foreign currency exchange rate fluctuations and currency controls;
- differing foreign reimbursement landscapes;
- uncertain and potentially inadequate reimbursement of our products; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

If risks related to any of these uncertainties materializes, it could have a material adverse effect on our business.

Risks Related to Our Intellectual Property

Our rights to develop and commercialize any product candidates are subject and may in the future be subject, in part, to the terms and conditions of licenses granted to us by third parties. If we fail to comply with our obligations under our current or future intellectual property license agreements or otherwise experience disruptions to our business relationships with our current or any future licensors, we could lose intellectual property rights that are important to our business.

We are and expect to continue to be reliant upon third-party licensors for certain patent and other intellectual property rights that are important or necessary to the development of our technology and product candidates. For example, we rely on licenses from the University of California, San Francisco, the University of Florida and the University of Missouri to certain patent rights. These license agreements impose, and we expect that any future license agreement will impose, specified diligence, milestone payment, royalty, commercialization, development and other obligations on us and require us to meet development timelines, or to exercise diligent or commercially reasonable efforts to develop and commercialize licensed products, in order to maintain the licenses.

Furthermore, our licensors have, or may in the future have, the right to terminate a license if we materially breach the agreement and fail to cure such breach within a specified period or in the event we undergo certain bankruptcy events. For example, such a termination may occur if we fail to meet specified development, regulatory and commercialization milestones by specified dates under our license agreements with the University of California, San Francisco, the University of Florida and the University of Missouri. In spite of our best efforts, our current or any future licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements. If our license agreements are terminated, we may lose our rights to develop and commercialize product candidates and technology, lose patent protection, experience significant delays in the development and commercialization of our product candidates and technology, and incur liability for damages. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, our competitors or other third parties could have the freedom to seek regulatory approval of, and to market, products and technologies identical or competitive to ours and we may be required to cease our development and commercialization of certain of our product candidates and technology. In addition, we may seek to obtain additional licenses from our licensors and, in connection with obtaining such licenses, we may agree to amend our existing licenses in a manner that may be more favorable to the licensors, including by agreeing to terms that could enable third parties, including our competitors, to receive licenses to a portion of the intellectual property that is subject to our existing licenses and to compete with any product candidates we may develop and our technology. Any of the foregoing could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- our or our licensors' ability to obtain, maintain and defend intellectual property and to enforce intellectual property rights against third parties;
- the extent to which our technology, product candidates and processes infringe, misappropriate or otherwise violate the intellectual property of the licensor that is not subject to the license agreement;
- the sublicensing of patent and other intellectual property rights under our license agreements;
- our diligence, development, regulatory, commercialization, financial or other obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our current or future licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, our license agreements are, and future license agreements are likely to be, complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our diligence, development, regulatory, commercialization, financial or other obligations under the relevant agreement. In addition, if disputes over intellectual property that we have licensed or any other dispute related to our license agreements prevent or impair our ability to maintain our current license agreements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates and technology. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

License agreements we may enter into in the future may be non-exclusive. Accordingly, third parties may also obtain non-exclusive licenses from such licensors with respect to the intellectual property licensed to us under such license agreements. Accordingly, these license agreements may not provide us with exclusive rights to use such licensed patent and other intellectual property rights, or may not provide us with exclusive rights to use such patent and other intellectual property rights in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and any product candidates we may develop in the future.

Moreover, some of our in-licensed patent and other intellectual property rights may in the future be subject to third-party interests such as co-ownership. If we are unable to obtain an exclusive license to such third-party co-owners' interest, in such patent and other intellectual property rights, such third-party co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. We or our licensors may need the cooperation of any such co-owners of our licensed patent and other intellectual property rights in order to enforce them against third parties, and such cooperation may not be provided to us or our licensors.

Additionally, we may not have complete control over the preparation, filing, prosecution, maintenance, enforcement and defense of patents and patent applications that we license from third parties. It is possible that our licensors' filing, prosecution and maintenance of the licensed patents and patent applications, enforcement of patents against infringers or defense of such patents against challenges of validity or claims of enforceability may be less vigorous than if we had conducted them ourselves, and accordingly, we cannot be certain that these patents and patent applications will be prepared, filed, prosecuted, maintained, enforced and defended in a manner consistent with the best interests of our business. If our licensors fail to file, prosecute, maintain, enforce and defend such patents and patent applications, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated, our right to develop and commercialize any of our technology and any product candidates we may develop that are the subject of such licensed rights could be adversely affected and we may not be able to prevent competitors or other third parties from making, using and selling competing products.

Furthermore, our owned and in-licensed patent rights may be subject to a reservation of rights by one or more third parties. When new technologies are developed with government funding, in order to secure ownership of patent rights related to the technologies, the recipient of such funding is required to comply with certain government regulations, including timely disclosing the inventions claimed in such patent rights to the U.S. government and timely electing title to such inventions. A failure to meet these obligations may lead to a loss of rights or the unenforceability of relevant patents or patent applications. In addition, the U.S. government may have certain rights in such patent rights, including a non-exclusive license authorizing the U.S. government to use the invention or to have others use the invention on its behalf. If the U.S. government decides to exercise these rights, it is not required to engage us as its contractor in connection with doing so. The U.S. government's

rights may also permit it to disclose the funded inventions and technology, which may include our confidential information, to third parties and to exercise march-in rights to use or allow third parties to use the technology that was developed using U.S. government funding. The U.S. government may exercise its march-in rights if it determines that action is necessary because we or our licensors failed to achieve practical application of the U.S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. These march-in rights would be applicable to our in-licensed patent rights relating to DB-OTO and potentially applicable to our in-licensed patent rights relating to AAV.104. In addition, our rights in such U.S. government-funded inventions may be subject to certain requirements to manufacture any product candidates we may develop embodying such inventions in the United States. Any of the foregoing could harm our business, financial condition, results of operations and prospects significantly.

If we are unable to obtain, maintain and defend adequate intellectual property protection and regulatory exclusivity for our products and technology, or if the scope of the intellectual property protection and regulatory exclusivity obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to ultimately successfully commercialize our products and technology may be adversely affected.

Our success depends, in large part, on our and our licensors' ability to obtain and maintain intellectual property protection in the United States and other countries with respect to our proprietary technology and product candidates. We and our licensors have sought, and we intend to continue to seek, to protect our proprietary position by filing patent and trademark applications in the United States and abroad related to many of our novel technologies and product candidates that are important to our business.

The patent prosecution process is expensive, time-consuming and complex, and we and our licensors may not be able to file, prosecute, maintain, defend, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. For example, in some cases, the work of certain academic researchers has entered the public domain, which may compromise our ability to obtain patent protection for certain inventions related to or building upon such prior work. Consequently, we may not be able to obtain any patents to prevent others from using such technology for, and developing and marketing competing products to treat, certain indications. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach these agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Consequently, we would not be able to prevent any third party from using any of our technology that is in the public domain to compete with any product candidates we may develop.

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. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future owned and licensed patent applications may not result in patents being issued which protect our technology or product candidates or which effectively prevent others from commercializing competitive technologies and product candidates. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Third parties have developed technologies that may be related or competitive to our own technologies and product candidates and may have filed or may file patent applications, or may have obtained issued patents, claiming inventions that may overlap or conflict with those claimed in our owned or licensed patent applications or issued patents. We may not be aware of all third-party intellectual property rights potentially relating to our product candidates and technology. Publications of discoveries in the scientific literature often lag the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we cannot be certain whether the inventors of our owned or licensed patents and patent applications were the first to make the inventions claimed in any owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. If a third party can establish that we or our licensors were not the first to make or the first to file for patent protection of such inventions, our owned or licensed patent applications may not issue as patents and even if issued, may be challenged and invalidated or ruled unenforceable.

Even if the patent applications we license or may own in the future do issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of patent rights, exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates.

In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Any of the foregoing could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

We also rely on regulatory exclusivity for protection of our products. Implementation and enforcement of regulatory exclusivity, which may consist of regulatory data protection and market protection, varies widely from country to country. Failure to qualify for regulatory exclusivity, or failure to obtain or maintain the extent or duration of such protections that we expect in each of the markets for our products due to challenges, changes or interpretations in the law or otherwise, could ultimately adversely affect our ability to successfully commercialize any products and technology.

We may not be successful in obtaining necessary rights to our product candidates through acquisitions and in-licenses. In addition, if we are unable to obtain licenses from third parties on commercially reasonable terms or fail to comply with our obligations under such agreements, our business could be harmed.

We currently have rights to certain intellectual property, through licenses from third parties, to develop and commercialize our product candidates. Because our programs may require the use of additional intellectual property rights held by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these intellectual property rights. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our product candidates.

The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program and develop and commercialize our product candidates.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly.

If we are unable to license such intellectual property, or if we are forced to license such intellectual property on unfavorable terms, our business could be materially harmed. If we are unable to obtain a necessary license, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales or an obligation on our part to pay royalties and/or other forms of compensation. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same intellectual property licensed to us, and the applicable licensors could require us to make substantial licensing and royalty payments.

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

Filing, prosecuting, maintaining, enforcing and defending patents and other intellectual property rights on our technology and any product candidates in all countries throughout the world would be prohibitively expensive, and our

intellectual property rights in some countries outside the United States could be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States.

Consequently, we and our licensors may not be able to obtain issued patents or other intellectual property rights covering our product candidates and our technology in all countries outside the United States and, as a result, may not be able to prevent third parties from practicing our and our licensors' inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we and our licensors have not obtained patent or other protection to develop their own products and, further, may export otherwise infringing, misappropriating or violating products to territories where we have patent or other intellectual property protection, but enforcement is not as strong as that in the United States. These products may compete with our products or technology and our or our licensors' patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Additionally, 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, misappropriation or other violation of our patent and other intellectual property rights or marketing of competing products in violation of our proprietary rights generally.

Proceedings to enforce our or our licensors' patent and other intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent and other intellectual property rights 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 or our licensors may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. We may choose not to initiate proceedings in certain cases or we may not have the resources to do so. 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.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

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

Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, 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 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. In the United States, 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 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. The European Union also provides for patent term extension through Supplementary Protection Certificates, or SPCs. The rules and requirements for obtaining a SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date but cannot extend the remaining term of a patent beyond a total of fifteen years from the marketing approval. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union. However, we may not be granted an extension because of lack of availability of extension or, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing 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 the 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.

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

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or patent applications will be due to be paid to the United States Patent and Trademark Office, or USPTO, and various government patent agencies outside of the United States over the lifetime of our owned or licensed patents and/or patent applications and any patent rights we may own in the future. We rely on our outside counsel and other professionals or our licensing partners to pay these fees due to the USPTO and non-U.S. government patent agencies. The USPTO and various non-U.S. government patent agencies also require compliance with several procedural, documentary and other similar provisions during the patent application process. We rely on our outside counsel and other professionals to help us comply and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment, loss of priority or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could harm our competitive positions, business, financial condition, results of operations and prospects.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged. We may not be able to protect our trade secrets in court.

If we or one of our licensors initiates legal proceedings against a third party to enforce a patent covering one of our product candidates or our technology, the defendant could counterclaim that the patent covering our product candidate or technology is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, lack of written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, interference proceedings, post grant review, inter partes review and equivalent proceedings such as opposition, invalidation and revocation proceedings in foreign jurisdictions. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our product candidates or our technology. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates or technology. Such a loss of patent protection could harm our business, financial condition, results of operations and prospects.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information, or technology that is not covered by patents. However, trade secrets can be difficult to protect, and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, contractors and other parties who have access to such technology and processes. However, 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. 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 collaborators, scientific advisors, employees and consultants who are parties to these agreements breach or violate 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 and third parties could use our trade secrets to compete with any product candidates we may develop and our technology. Additionally, we cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems; however, such systems and security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered.

Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could harm our business.

Our commercial success depends upon our ability and the ability of our collaborators to research, develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights.

It is possible that we have failed to identify relevant third-party patents or applications that our product candidates and programs may infringe. 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 any product candidates we may develop or our technology, and we may not be aware of such patents. Furthermore, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States may remain confidential until a patent issues. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to any product candidates we may develop and our 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 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, any product candidates we may develop or the use of any product candidates we may develop.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. For example, we are aware of a third-party U.S. patent relating to certain otoferlin dual vector constructs and the uses thereof that contains claims that cover DB-OTO and could be asserted against us by the third party. We believe that we would have valid defenses to any such claims and would vigorously defend any such claims. However, we may not be successful. There is a risk that a third party or others may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could adversely affect our ability to commercialize our product candidates or any other of our product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe, misappropriate or otherwise violate a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product candidates and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidates. 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 or other intellectual property right and may be required to indemnify our customers or collaborators. A finding of infringement could prevent us from manufacturing and commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

Intellectual property litigation or other proceedings relating to intellectual property could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Competitors may challenge the validity and enforceability of our patent rights or those of our licensing partners, infringe, misappropriate or otherwise violate our or our licensors' patent and other intellectual property rights, or we may be required to defend against claims of infringement, misappropriation or other violation. Litigation and other proceedings in connection with any of the foregoing claims can be unpredictable, expensive and time-consuming. Even if resolved in our favor, litigation or other proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of intellectual property litigation or other proceedings could adversely affect our ability to compete in the marketplace and could 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 or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, 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. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or be required to obtain licenses to such intellectual property rights, which may not be available on commercially reasonable terms or at all. An inability to incorporate such intellectual property rights would harm our business and may prevent us from successfully commercializing any product candidates we may develop or at all. In addition, we may lose personnel as a result of such claims and any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent contractors. A loss of key personnel or their work product could hamper or prevent our ability to commercialize any product candidates we may develop and our technology, which would have a material adverse effect on our business, results of operations, financial condition and prospects. 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, contractors and advisors 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.

In addition, we or our licensors may in the future be subject to claims by former employees, consultants or other third parties asserting an ownership right in our owned or licensed patent rights. An adverse determination in any such submission or proceeding may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar technology and therapeutics, without payment to us, or could limit the duration of the patent protection covering our technology and any product candidates we may develop. Such challenges may also result in our inability to develop, manufacture or commercialize our technology and product candidates without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our owned or licensed patent rights are threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future technology and product candidates. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

Changes in patent law in the United States or worldwide could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of patent laws in the United States and worldwide, including patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of our owned and in-licensed patent applications and the maintenance, enforcement or defense of our owned and in-licensed issued patents. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, inter partes review, and derivation proceedings. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which,

assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. 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. This combination of events has created uncertainty with respect to the validity and enforceability of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patents, trade secrets or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing any product candidates or technology. Litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in-licensed patents, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could have a material adverse effect on our competitive business position and prospects. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products, which license may not be available on commercially reasonable terms, or at all, or such license may be non-exclusive. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Any registered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our business, financial condition, results of operations or prospects.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products that are similar to our product candidates but that are not covered by the claims of the patents that we license or own currently or in the future;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent applications that we license or own currently or in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating our owned or in-licensed intellectual property rights;

- it is possible that our pending patent applications or those that we may own or in-license in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by third parties;
- third parties might conduct research and development activities in countries where we do not have patent or other intellectual property rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we cannot ensure that any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect our product candidates;
- we cannot ensure that any patents issued to us will provide a basis for an exclusive market for our commercial viable product candidates or will provide us with any competitive advantages;
- we cannot ensure that our commercial activities or product candidates will not infringe upon the patents of others;
- we may not develop additional proprietary technologies that are patentable;
- we cannot ensure that we will be able to successfully commercialize our product candidates on a substantial scale, if approved, before our relevant patents expire;
- the patents or other intellectual property rights of others may have an adverse effect on our business; and
- we may choose not to file a patent for certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we currently rely on certain third parties to manufacture all or part of our product candidates and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our product engine and pipeline, we must, at times, share our proprietary technology and confidential information, including any trade secrets we have, with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements and, if applicable, material transfer agreements, sponsored research agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors or other third parties, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and any trade secrets we have, a competitor's discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may harm our business, financial condition, results of operations and prospects.

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets by third parties. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

Risks Related to Regulatory Approval and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming, and uncertain and may prevent us from obtaining approvals for the commercialization of any product candidates we develop. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize, or will be delayed in commercializing, product candidates we develop, and our ability to generate revenue will be materially impaired.

Any product candidates we develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States, and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity and potency or the drug product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any product candidates we develop 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.

The process of obtaining marketing approvals, both in the United States and outside the United States, is expensive, may take many years if additional clinical trials are required, 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. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is 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. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved medicine not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of any product candidates we develop, the commercial prospects for those product candidates may be harmed, and our ability to generate revenues will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent any product candidates we develop from being marketed in such jurisdictions, which, in turn, would materially impair our ability to generate revenue.

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

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the withdrawal of the United Kingdom from the European Union, commonly referred to as Brexit. The United Kingdom is no longer part of the European Single Market and European Union Customs Union. As of January 1, 2021, the MHRA became responsible for supervising medicines and medical devices in Great Britain, comprising of England, Scotland and Wales, under domestic law, whereas Northern Ireland will continue to be subject to European Union rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or

the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the body of European Union law instruments governing medicinal products that pre-existed prior to the United Kingdom's withdrawal from the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for our product candidates, which could significantly and materially harm our business. Since a significant proportion of the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom. For example, the United Kingdom is no longer covered by the centralized procedures for obtaining European Union-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market our product candidates in the United Kingdom. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission on the approval of a new marketing authorization via the centralized procedure.

Regulatory requirements governing gene therapy products are periodically updated and may continue to change in the future.

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. For example, the FDA has established the Office of Tissues and Advanced Therapies (formerly the Office of Cellular, Tissue and Gene Therapies) within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Additionally, gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from NIH also are potentially subject to oversight by a committee within the NIH's Office of Science Policy called the Novel and Exceptional Technology and Research Advisory Committee; however, as of 2019, the charter of this review group has evolved to focus public review on clinical trials that cannot be evaluated by standard oversight bodies and pose unusual risks.

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, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these 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 our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

The FDA decides whether individual gene therapy protocols may proceed and it can put an IND on a clinical hold. If we were to engage an NIH-funded institution to conduct a clinical trial, that institution's IRB would need to review the proposed clinical trial to assess the safety of the trial. In addition, 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 our product candidates. Similarly, the EMA may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines.

In addition, ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed their intentions to further regulate biotechnology. More restrictive regulations or claims that our product candidates are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

As we advance our product candidates through clinical development, we will be required to consult with these regulatory and advisory groups, and comply with applicable guidelines. These regulatory review committees and advisory groups and any new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, 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. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue.

We may seek fast track, breakthrough therapy, and/or regenerative medicine advanced therapy designations or priority review for one or more of our product candidates, but we might not receive such designation or priority review, and even if we do, such designation or priority review may not lead to a faster development or regulatory review or approval process, and does not assure FDA approval of our product candidates.

The FDA has several designations that have the potential to accelerate the regulatory review and approval process, including the fast track, breakthrough therapy and regenerative medicine advanced therapy designations. Each of these designations has specific requirements and, if granted, has the potential for a non-conventional FDA review process. The FDA has granted fast track designation for DB-020 for the prevention of cisplatin-related ototoxicity. In addition, if the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. Any such designation or priority review status does not ensure that the product candidate will receive marketing approval or that approval will be granted within any particular timeframe. As a result, while we may seek and receive one or more of these designation for our product candidates, we may not experience a faster development process, review, or approval compared to conventional FDA procedures. The FDA has broad discretion with respect to whether or not to grant such designations or priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. In addition, the FDA may withdraw a designation if it believes that the designation is no longer supported by data from our clinical development program. Moreover, fast track, breakthrough therapy, or regenerative medicine advanced therapy designations alone do not guarantee qualification for the FDA's priority review procedures. Nor do they assure approval of any of our candidate products.

We may seek PRIME Designation in the European Union for one or more of our product candidates but we might not receive such designations and, even if we do, such designations may not lead to a faster development or regulatory review or approval process.

In the European Union, we may seek PRIME designation for our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the European Union or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the European Union and the applicant intends to apply for an initial marketing authorization application through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria in respect of its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims.

The benefits of a PRIME designation include the appointment of a Committee for Human Medicinal Products rapporteur to provide continued support and help to build knowledge ahead of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

We have been granted rare pediatric disease designation for our lead gene therapy product candidate, DB-OTO, and we may seek a rare pediatric disease designation for one or more of our other product candidates. However, DB-OTO and any of our other product candidates that may be granted a rare pediatric disease designation may not meet the eligibility criteria for a priority review voucher upon approval.

With enactment of the Food and Drug Administration Safety and Innovation Act in 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications that meet the criteria specified in the law. This provision is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases.

Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. A priority review voucher

for priority review authorizes review of a marketing application in six months, compared to the standard timeframe of approximately 10 months.

For the purposes of this program, a "rare pediatric disease" is a (i) serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (ii) rare disease or conditions within the meaning of the Orphan Drug Act. The FDA may determine that an application for one or more of our product candidates does not meet the eligibility criteria for a priority review voucher upon approval.

Moreover, while the opportunity to receive a priority review voucher was meant to expire for those companies that had not received a designation by September 30, 2020, Congress authorized an extension of the program in late 2020. Specifically, on December 27, 2020, the Rare Pediatric Disease Priority Review Voucher Program was extended. Under the current statutory sunset provisions, after September 30, 2024, the FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug or biologic that is the subject of such application, and that designation was granted by September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease priority review vouchers.

The FDA has granted rare pediatric disease designation for DB-OTO for the treatment of OTOF-related, congenital hearing loss. We cannot be certain that we will receive approval for this product candidate or any other of our rare pediatric disease designated product candidates prior to the statutory sunset date, if ever. Moreover, even if we believe that our marketing application meets the other requirements to be eligible to receive a priority review voucher upon approval, the FDA may disagree. Further, if we do not obtain approval of our application for DB-OTO for of OTOF-related, congenital hearing loss by the applicable dates, and if the Priority Review Voucher Program is not further extended by congressional action, we may not receive a priority review voucher.

We have been granted orphan drug designation for our lead gene therapy product candidate, DB-OTO. We may not be able to obtain orphan drug exclusivity for one or more of our other product candidates, and even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.

We received orphan drug designation for DB-OTO in the United States. We may seek orphan drug designation in other indications or for any other product candidates we develop. Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition. A similar regulatory scheme governs approval of orphan products by the EMA in the European Union. Generally, if a product candidate with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same product for the same therapeutic indication for that time period. The applicable period is seven years in the United States and ten years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation, in particular if the product is sufficiently profitable so that market exclusivity is no longer justified.

In order for the FDA to grant orphan drug exclusivity to one of our products, the FDA must find that the product is indicated for the treatment of a condition or disease with a patient population of fewer than 200,000 individuals annually in the United States. The FDA may conclude that the condition or disease for which we seek orphan drug exclusivity does not meet this standard. Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. In particular, with respect to the concept of what constitutes the "same drug" for purposes of orphan drug exclusivity in the context of gene therapies, the FDA issued final guidance in September 2021 suggesting that it would not consider two gene therapy products to be different drugs solely based on minor differences in the transgenes or vectors within a given vector class.

In addition, even after an orphan drug is approved, the FDA can subsequently approve the same product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA, MHRA, or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of the patients with the rare disease or condition. Further, if our gene therapy product candidate is considered the "same" as another product for the same indication, and the other product is designated as an orphan drug and receives approval first, our product would be blocked from approval by the orphan drug exclusivity afforded to the other product unless it qualifies for an exception to that exclusivity.

In 2017, the Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an

orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. Moreover, in the Consolidated Appropriations Act of 2021, Congress did not further change this interpretation when it clarified that the interpretation codified in FDARA would apply in cases where the FDA issued an orphan designation before the enactment of FDARA but where product approval came after the enactment of FDARA.

The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11th Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Although there have been legislative proposals to overrule this decision, they have not been enacted into law. On January 23, 2023, the FDA announced that, in matters beyond the scope of that court order, the FDA will continue to apply its existing regulations tying orphan-drug exclusivity to the uses or indications for which the orphan drug was approved. We do not know if, when, or how the FDA or Congress may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

We are conducting, and intend in the future to conduct, clinical trials for certain of our product candidates at sites outside the United States. The FDA may not accept data from trials conducted in such locations and the conduct of trials outside the United States could subject us to additional delays and expense.

We are conducting, and intend in the future to conduct, one or more of our clinical trials with trial sites that are located outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to certain conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with good clinical practice. The FDA must be able to validate the data from the trial through an onsite inspection if necessary. The trial population must also have a similar profile to the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful, except to the extent the disease being studied does not typically occur in the United States. In addition, while these clinical trials are subject to the applicable local laws, the FDA acceptance of the data will be dependent upon its determination that the trials also complied with all applicable U.S. laws and regulations. There can be no assurance that the FDA will accept data from clinical trials conducted outside of the United States. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and delay our development of our product candidates.

In addition, the conduct of clinical trials outside the United States could have a significant adverse impact on us or the trial results. Risks inherent in conducting international clinical trials include:

- clinical practice patterns and standards of care that vary widely among countries;
- non-U.S. regulatory authority requirements that could restrict or limit our ability to conduct our clinical trials;
- administrative burdens of conducting clinical trials under multiple non-U.S. regulatory authority schema;
- foreign exchange rate fluctuations; and
- diminished protection of intellectual property in some countries.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate or the approval may be for a narrower indication than we expect.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies 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 agency policy during the period of product development, clinical trials and the review process. Regulatory agencies also may approve a treatment candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing commitments. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization

of our treatment candidates. For example, the development of our product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer.

Even if we, or any collaborators we may have, obtain marketing approvals for any product candidates we develop, the terms of approvals and ongoing regulation of our products could require the substantial expenditure of resources and may limit how we, or they, manufacture and market our products, which could materially impair our ability to generate revenue.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising, and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. For example, the holder of an approved application is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. For gene therapies that use AAV vectors as a delivery system, the FDA typically advises that individuals receiving AAV vectors undergo follow-up observations for potential adverse events for up to a five-year period. The holder of an approved application must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling, or manufacturing process. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine.

Accordingly, assuming we, or any collaborators we may have, receive marketing approval for one or more product candidates we develop, we, and such collaborators, and our and their contract manufacturers will continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance, and quality control. If we and such collaborators are not able to comply with post-approval regulatory requirements, we and such collaborators could have the marketing approvals for our products withdrawn by regulatory authorities and our, or such collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our business, results of operations, financial condition and prospects.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or supplements to a BLA submitted by us;
- seize product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenues.

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

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of medicines to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our medicines for their approved indications, we may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the Department of Justice. Violation of the Federal Food, Product, and Cosmetic Act and other statutes, including the False Claims Act, relating to the

promotion and advertising of prescription products may also lead to investigations or allegations of violations of federal and state healthcare fraud and abuse laws and state consumer protection laws. In September 2021, the FDA published final regulations which describe the types of evidence that the FDA will consider in determining the intended use of a drug product.

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

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

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize any product candidates we develop and adversely affect our business, financial condition, results of operations, and prospects.

Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a REMS to ensure that the benefits 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 healthcare 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 on the label;
- 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.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs applicable to drug manufacturers or quality assurance standards applicable to medical device manufacturers, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, any contract manufacturers we may engage in the future, our future collaborators and their contract manufacturers will also be subject to other regulatory requirements, including submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements regarding the distribution of samples to clinicians, recordkeeping, and costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product such as the requirement to implement a REMS.

Similar restrictions apply to the approval of our products in the European Union. The holder of a marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and

sale of medicinal products. These include: compliance with the European Union's stringent pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations; the manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory; and the marketing and promotion of authorized drugs, which are strictly regulated in the European Union and are also subject to European Union Member State laws. The failure to comply with these and other European Union requirements can also lead to significant penalties and sanctions.

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

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

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving, or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward 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 and state healthcare programs such as Medicare and Medicaid;
- the federal false claims laws, including the federal False Claims Act which can be enforced through civil whistleblower or qui tam actions, impose criminal and civil penalties against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid, or other government payors 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, as further amended by the Health Information Technology for Economic and Clinical Health Act, which imposes certain requirements, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, healthcare clearinghouses, and certain healthcare providers as well as their respective business associates that perform services for them that involve the use or disclosure of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services;
- the federal transparency requirements under the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics, and medical supplies to report to the U.S. Department of Health and Human Services, or HHS, information related to payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and certain state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures; and state and local laws that require drug manufacturers to register pharmaceutical sales representatives.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order, or use of medicinal products is prohibited in the European Union and the United Kingdom. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of European Union Member States and the U.K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or

her competent professional organization, and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

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, disgorgement, exclusion from government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our business, financial condition, results of operations, and prospects. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to significant criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs. Liabilities they incur pursuant to these laws could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

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

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any products for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any future collaborators, may receive for any approved products.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or the PPACA, which became law in 2010, contains the following provisions of importance to our business, including, without limitation, our ability to commercialize and the prices we may obtain for any of our product candidates that are approved for sale:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of federal healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program new requirements to report financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2029 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three

to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and executive and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the TCJA, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Further, the Bipartisan Budget Act of 2018, among other things, amended the PPACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." More recently, the CARES Act, which was signed into law on March 27, 2020 and designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester until 2031. Medicare sequester reductions were suspended and reduced between May 1, 2020 until June 30, 2022, but the full 2% cut resumed thereafter. With passage of the Inflation Reduction Act in August 2022, Congress extended the expansion of PPACA premium tax credits through 2025. Those subsidies were originally extended through 2022 under the American Rescue Plan Act of 2021.

The Trump Administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Executive Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

Current and future legislative efforts may limit the costs for our products, if and when they are licensed for marketing, and that could materially impact our ability to generate revenues.

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. There have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, and reduce the costs of pharmaceuticals under Medicare and Medicaid. In 2020, President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, Centers for Medicare & Medicaid Services, or CMS, issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In addition, in October 2020, the HHS, and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. The final rule is currently the subject of ongoing litigation, but at least six states (Vermont, Colorado, Florida, Maine, New Mexico and New Hampshire) have passed laws allowing for the importation of drugs from Canada with the intent of developing SIPs for review and approval by the FDA. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2026 by the Infrastructure Investment and Jobs Act. Congress continues to consider various legislative measures to limit the costs of prescription drugs, including authorizing Medicare to negotiate the prices of certain pharmaceuticals with

manufacturers each year, capping beneficiary out-of-pocket Part D drug costs at $2,000 a year, and penalizing drug manufacturers for price hikes that outpace inflation.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least nine years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. The new law also caps Medicare out-of-pocket drug costs at an estimated $4,000 a year in 2024 and, thereafter beginning in 2025, at $2,000 a year. In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or "catastrophic period" of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period, must pay 100% of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co-insurance and co-payment costs, expanding eligibility for lower income subsidy plans, and price caps on annual out-of-pocket expenses, each of which could have potential pricing and reporting implications.

Accordingly, while it is currently unclear how the IRA will be effectuated, we cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. 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, which could result in reduced demand for our products or additional pricing pressures.

Outside the United States, in some countries, including those of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control and access. 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 or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment

methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our potential products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

The commercial success of our products depends on the availability and sufficiency of third-party payor coverage and reimbursement.

Our ability to commercialize any products successfully will depend in part on the extent to which coverage and adequate reimbursement for such products will be available from third-party payors. Even if we succeed in bringing one or more products to the market, these products may not be considered cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. Because our programs are in the early stages of development, we are unable at this time to determine their cost-effectiveness or the likely level or method of coverage and reimbursement.

Further, no uniform policy for coverage and reimbursement exists in the United States, and coverage and reimbursement can differ significantly from payor to payor. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. As such, one third-party payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. Additionally, we may develop companion diagnostic tests for use with our product candidates. If we do, we will be required to obtain coverage and reimbursement for these tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved. While we have not yet developed any companion diagnostic test for our product candidates, if we do, there is significant uncertainty regarding our ability to obtain coverage and adequate reimbursement for the same reasons applicable to our product candidates. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for our products and/or any companion diagnostics could have a material and adverse effect on our business, financial condition, results of operations, and prospects.

Our employees, principal investigators, consultants, and commercial partners 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, consultants, and partners, and, if we commence clinical trials, our principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union and other jurisdictions, provide accurate information to the FDA, the European Commission, and other regulatory authorities, 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 restrict or prohibit a wide range of pricing, discounting, marketing, and promotion, sales commission, customer incentive programs, and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, 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 government 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, financial condition, results of operations, and prospects, including the imposition of significant fines or other sanctions.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates outside of the United States and require us to develop and implement costly compliance programs.

We are subject to numerous laws and regulations in each jurisdiction outside the United States in which we operate. The creation, implementation and maintenance of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required.

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

Compliance with the FCPA and other anti-corruption laws potentially applicable to our business is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the compliance with the FCPA and other anti-corruption laws presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions.

We are also subject to other laws and regulations governing our international operations, including applicable export control laws, economic sanctions on countries and persons, and customs requirements. In addition, various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. Our expansion outside of the United States has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain drugs and drug candidates outside of the United States, which could limit our growth potential and increase our development costs.

There is no assurance that we will be completely effective in ensuring our compliance with the FCPA and other applicable anti-corruption, export, sanctions, and customs laws. The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violations of these laws, including the FCPA, can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the European Union General Data Protection Regulation, or the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater and it 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. In addition, the GDPR provides that European Union member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Similar actions are either in place or under way in the United States. There are a broad variety of data protection laws that are applicable to our activities, and a wide range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act—which went into effect on January 1, 2020—is creating similar risks and obligations as those created by GDPR, though the Act does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with federal and state laws (both those currently in effect and future legislation) regarding privacy and security of personal information could expose us to fines and penalties under such laws. There also is the threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with these requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the European Union. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations.

If approved, our product candidates that are licensed and regulated as biologics may face competition from biosimilars approved through an abbreviated regulatory pathway.

The Biologics Price Competition and Innovation Act of 2009, or BPCIA, was enacted as part of PPACA, to establish an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The 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 approved biologic. Under the BPCIA, a reference biological product is granted 12 years of data exclusivity from the time of first licensure of the product, and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product In addition, the licensure of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still develop and receive approval of a competing biologic, so long as its BLA does not reply on the reference product, sponsor's data or submit the application as a biosimilar application. 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, and any new policies or processes adopted by the FDA could have a material adverse effect on the future commercial prospects for our biological products.

We believe that any of the product candidates we develop as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider the subject product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of the reference products in a way that is similar to traditional generic substitution for non-biological products will depend on a number of marketplace and regulatory factors that are still developing. Nonetheless, the approval of a biosimilar to our product candidates would have a material adverse impact on our business due to increased competition and pricing pressure.

Risks Related to Employee Matters, Managing Growth and General Business Operations

The COVID-19 pandemic, which began in late 2019 and spread worldwide, disrupted our ongoing Phase 1b clinical trial of DB-020 and has affected and may in the future affect our ability to initiate and complete preclinical studies, delay the

initiation of our planned clinical trials or future clinical trials, disrupt regulatory activities, disrupt our manufacturing and supply chain or have other adverse effects on our business and operations. In addition, this pandemic has caused substantial disruption to global supply chains and has and may continue to adversely impact economies worldwide, both of which could result in adverse effects on our business, operations and ability to raise capital.

The COVID-19 pandemic, which began in December 2019 and spread worldwide, has caused many governments to implement measures to slow the spread of COVID-19 through quarantines, travel restrictions, heightened border scrutiny and other measures. The COVID-19 pandemic and government measures taken in response have also had a significant impact, both directly and indirectly, on businesses and commerce, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen.

While the COVID-19 pandemic has not materially impacted our business to date, there is no guarantee that it, or its impact on the global economy, will not materially impact our business in the future. We cannot provide assurance that some factors from the COVID-19 pandemic will not delay or otherwise adversely affect our clinical development, research, manufacturing and business operations activities, as well as our business generally, in the future. For example, screening and enrollment in our Phase 1b clinical trial of DB-020 in Australia and the United States was adversely impacted by the COVID-19 pandemic in 2020. In addition, we and the third-party manufacturers, CROs and academic collaborators that we engage have faced in the past and may face in the future disruptions that could affect our ability to initiate and complete preclinical studies or clinical trials. For example, due to increased quarantine mandates in China, the receipt of shipments and data from some of our vendors and CROs were more difficult and unpredictable during the first half of 2022. This caused some delays in preclinical studies for our gene therapy programs.

The pandemic has already caused significant disruptions to global supply chains, adverse impacts to economies worldwide and disruptions to financial markets. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business and it has the potential to adversely affect our business, financial condition, results of operations, and prospects.

On January 30, 2023, the Biden Administration announced that it will end the public health emergency declarations related to COVID-19 on May 11, 2023. On January 31, 2023, the FDA indicated that it would soon issue a Federal Register notice describing how the termination of the public health emergency will impact the agency's COVID-19 related guidances, including the clinical trial guidance and updates thereto. At this point, it is unclear how, if at all, these developments will impact our efforts to develop and commercialize our product candidates.

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, financial, operational and other business expertise of our executive officers, as well as the other principal members of our management, scientific and clinical teams. Although we have entered into 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. Recruiting and retaining qualified scientific, clinical, manufacturing, accounting, legal and sales and marketing personnel will also be critical to our success.

The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain marketing approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization 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. Our success as a public company also depends on implementing and maintaining internal controls and the accuracy and timeliness of our financial reporting. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

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

As we seek to advance our product candidates through clinical trials and commercialization, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, clinical, regulatory affairs and, if any product candidate receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our internal computer systems, or those used by our CROs, CDMOs or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our current and any future CROs, CDMOs or other contractors or consultants, including any collaborator, are vulnerable to damage from cyber-attacks, computer viruses, worms and other destructive or disruptive software, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Cyber incidents or attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber incidents also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. System failures, accidents, cyberattacks or security breaches could 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, in addition to possibly requiring substantial expenditures of resources to remedy. The loss of preclinical or clinical trial data from completed or future preclinical studies or clinical trials could result in delays in regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential, personal or proprietary information, we could incur liability, including civil fines and penalties under relevant state and federal privacy laws in the United States and abroad, our competitive position could be harmed and the further development of our product candidates and programs could be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

While we have not experienced any material losses relating to cyber-attacks, we have been the subject of a successful phishing attempt. We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees. In addition, outside parties may attempt to penetrate our systems or those of our CROs, CDMOs or other contractors or consultants or fraudulently induce our employees or employees of our CROs, CDMOs or other contractors or consultants to disclose sensitive information in order to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our security or that of our CROs, CDMOs or other contractors or consultants occurs, the market perception of the effectiveness of our security measures could be harmed, and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, 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 more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely.

Our operations or those of the third parties upon whom we depend might be affected by the occurrence of a natural disaster, pandemic or other catastrophic event.

We depend on our employees, consultants, CDMOs and CROs, as well as regulatory agencies and other parties, for the continued operation of our business. While we maintain disaster recovery plans, they might not adequately protect us. Despite any precautions we take for natural disasters or other catastrophic events, these events, including terrorist attack, pandemics, hurricanes, fire, floods and ice and snowstorms, could result in significant disruptions to our research and development, preclinical studies, clinical trials, and, ultimately, commercialization of our products. Long-term disruptions in

the infrastructure caused by events, such as natural disasters, the outbreak of war, the escalation of hostilities and acts of terrorism or other "acts of God," particularly involving cities in which we have offices, manufacturing or clinical trial sites, could adversely affect our businesses. Although we carry business interruption insurance policies and typically have provisions in our contracts that protect us in certain events, our coverage might not respond or be adequate to compensate us for all losses that may occur. Any natural disaster or catastrophic event affecting us, our CDMOs or CROs, regulatory agencies or other parties with which we are engaged could have a significant negative impact on our operations and financial performance.

Risks Related to Ownership of Our Common Stock and Our Status as a Public Company

An active trading market for our common stock may not develop or be sustained.

Although our common stock is listed on the Nasdaq Global Select Market, an active trading market for our shares may never develop or be sustained. As a result, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or at all.

If securities analysts do not publish or cease publishing research or reports or publish misleading, inaccurate or unfavorable research about our business or if they publish negative evaluations of our stock, the price and trading volume 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 control over these analysts. There can be no assurance that existing analysts will continue to cover us or that new analysts will begin to cover us. There is also no assurance that any covering analyst will provide favorable coverage. Although we have obtained analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, or provide more favorable relative recommendations about our competitors, 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 and trading volume to decline.

The price of our common stock is likely to be volatile and fluctuate substantially, which could result in substantial losses for our stockholders.

Our stock price has been, and is likely to continue to be, volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price they paid for their shares. The market price for our common stock may be influenced by many factors, including:

- results of or developments in preclinical studies and clinical trials of our product candidates or those of our competitors or potential collaborators;
- timing of the results of our preclinical studies and clinical trials or those of our competitors;
- our success in commercializing our product candidates, if and when approved;
- developments with respect to competitive products or technologies;
- regulatory or legal developments in the United States and other countries;
- events involving limited liquidity, defaults, non-performance or other adverse developments that affect companies in the financial services industry or the financial services industry generally;
- developments or disputes concerning patent applications, issued patents or other intellectual property or 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 products, product candidates, technologies, or data referencing rights, the costs of commercializing any such products and the costs of development of any such product candidates or technologies;

- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or the financial results of companies that are perceived to be similar to us;
- sales of common stock by us, our executive officers, directors or principal stockholders or others;
- changes in the structure of healthcare payment systems;
- market conditions in the biopharmaceutical and biotechnology sectors;
- general economic, industry and market conditions, such as the impact of the COVID-19 pandemic on our industry; and
- the other factors described in this "Risk Factors" section.

In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation has often been instituted against that company. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our offerings or business practices. Such litigation may also cause us to incur other substantial costs to defend such claims and divert management's attention and resources.

Our executive officers and directors and their affiliates, if they choose to act together, have the ability to significantly influence all matters submitted to stockholders for approval.

As of March 1, 2023, our executive officers and directors and their affiliates, in the aggregate, beneficially owned shares of common stock representing approximately 35.5% of our common stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these stockholders, if they choose to act together, would significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and board of directors; or
- delay or prevent a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

We have broad discretion in the use of our cash, cash equivalents and available-for-sale securities and may not use them effectively.

Our management has broad discretion in the application of cash, cash equivalents and available-for-sale securities and could spend them in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the advancement of our product candidates. Pending their use, we may invest these funds in a manner that does not produce income or that loses value.

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

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth of our business. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

A significant portion of our total outstanding shares are eligible to be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. As of March 1, 2023, we had 25,014,984 shares of common stock outstanding. All of our outstanding shares of common stock are

available for sale in the public market, subject only to the restrictions of Rule 144 under the Securities Act of 1933, as amended, or the Securities Act, in the case of our affiliates.

Moreover, holders of an aggregate of 6,418,211 shares of our common stock have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We also registered all shares of common stock that we may issue under our equity compensation plans.

These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

We are an "emerging growth company" and a "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," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an EGC until December 31, 2026, although if the market value of our common stock that is held by non-affiliates exceeds $700 million as of any June 30 before that time or if we have annual gross revenues of $1.235 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than $1 billion of non-convertible debt over a three-year period. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not EGCs. These exemptions include:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

Even after we no longer qualify as an emerging growth company, we may continue to qualify as a smaller reporting company, which would allow us to take advantage of many of the same exemptions from disclosure requirements, including reduced disclosure obligations regarding executive compensation. In addition, if we are a smaller reporting company with less than $100 million in annual revenue, we would not be required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404. We may choose to take advantage of some, but not all, of the available exemptions.

In addition, the JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have elected to take advantage of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we will adopt the new or revised standard at the time private companies adopt the new or revised standard and will do so until such time that we either irrevocably elect to "opt out" of such extended transition period or no longer qualify as an EGC. We may choose to early adopt any new or revised accounting standards whenever such early adoption is permitted for private companies.

We cannot predict whether investors will find our common stock less attractive if we rely on certain or all of 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.

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

As a public company, and particularly after we are no longer an EGC or a smaller reporting company, we have incurred and will continue to incur significant legal, accounting and other expenses that we did not previously incur as a private company. The Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective

disclosure and financial controls and corporate governance practices. Our management and other personnel devote and will continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs, particularly as we hire additional financial and accounting employees to meet public company internal control and financial reporting requirements, and will make some activities more time-consuming and costly compared to when we were a private company.

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

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting on an annual basis. However, while we remain an EGC or a smaller reporting company with less than $100 million in annual revenue, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, including through hiring additional financial and accounting personnel, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. During our evaluation of our internal control, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, stockholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could harm our business and have a negative effect on the trading price of our stock.

We are required to disclose changes made in our internal controls and procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an EGC under the JOBS Act or a smaller reporting company with less than $100 million in annual revenue, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404. We may remain an EGC until December 31, 2026. Our assessment of internal controls and procedures may not detect material weaknesses in our internal control over financial reporting. Undetected material weaknesses in our internal control over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation, which could have a negative effect on the trading price of our stock.

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

Provisions in our certificate of incorporation and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these

provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that only one of three classes of directors is elected each year;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from our board of directors;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "poison pill" that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal specified provisions of our certificate of incorporation or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or 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.

Our certificate of incorporation designates the Court of Chancery of the State of Delaware and the federal district courts of the United States of America as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers and employees.

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders;
- any action asserting a claim arising pursuant to any provision of the DGCL or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware; or
- any action asserting a claim arising pursuant to any provision of our certificate of incorporation or bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine.

These choice of forum provisions will 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. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

These exclusive forum provisions may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees. If a court were to find either exclusive forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur further significant additional costs associated with resolving such action in other jurisdictions, all of which could materially adversely affect our business, financial condition and results of operations.

General Risk Factors

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized, and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Changes in tax law may adversely affect our business or financial condition. The TCJA, as amended by the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, contained significant changes to corporate taxation, including reducing the corporate tax rate from a top marginal rate of 35% to a flat rate of 21% and limiting the deduction for NOLs to 80% of current year taxable income for losses arising in taxable years beginning after December 31, 2017 (though any such NOLs may be carried forward indefinitely). In addition, beginning in 2022, the TCJA eliminates the option to deduct research and development expenditures currently and requires corporations to capitalize and amortize them over five years.

In addition to the CARES Act, as part of Congress' response to the COVID-19 pandemic, economic relief legislation was enacted in 2020 and 2021 containing tax provisions. The IRA was also signed into law in August 2022. The IRA introduced new tax provisions, including a one percent excise tax imposed on certain stock repurchases by publicly traded companies. The one percent excise tax generally applies to any acquisition of stock by the publicly traded company (or certain of its affiliates) from a stockholder of the company in exchange for money or other property (other than stock of the company itself), subject to a de minimis exception. Thus, the excise tax could apply to certain transactions that are not traditional stock repurchases.

Regulatory guidance under the TCJA, the IRA and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. In addition, it is uncertain if and to what extent various states will conform to the TCJA, the IRA and such additional legislation.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal facilities consist of office and laboratory space. We occupy approximately 32,000 square feet of office and laboratory space in Boston, Massachusetts under a lease that expires in June 2027. We also occupy approximately 17,000 square feet of office space in Boston, Massachusetts under a sublease that expires in January 2027. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently subject to any material legal proceedings. Regardless of outcome, litigation can have an adverse impact on our

business, financial condition, results of operations, cash flows and prospects because of defense and settlement costs, diversion of management resources 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 for Our Common Stock

Our common stock trades under the symbol "DBTX" on the Nasdaq Global Select Market and has been publicly traded since February 12, 2021. Prior to this time, there was no public market for our common stock.

Holders of Record of Our Common Stock

As of March 1, 2023, there were approximately 86 holders of record of shares of our common stock. The actual number of stockholders is greater than this number of holders of record 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 have never declared nor paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to declare and pay dividends will be made at the discretion of our board of directors and will depend on then-existing conditions, including our results of operations, financial condition, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Securities Authorized for Issuance Under Equity Compensation Plans

The information required by this item is set forth in "Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters" and is incorporated herein by reference.

Use of Proceeds from Registered Securities

On February 17, 2021, we closed our initial public offering, or IPO, in which we issued and sold 7,062,000 shares of our common stock at a public offering price of $18.00 per share, and on February 24, 2021, we issued and sold an additional 600,000 shares pursuant to the underwriters' partial exercise of their option to purchase additional shares, for aggregate gross proceeds of $137.9 million. All of the shares of common stock issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (Registration No. 333-252347), which was declared effective by the SEC on February 11, 2021.

The aggregate net proceeds to us from the public offering, inclusive of the proceeds from the underwriters' partial exercise of their option to purchase additional shares, was approximately $124.8 million, after deducting underwriting discounts and commissions and other offering expenses payable by us of approximately $13.1 million.

As of December 31, 2022, we have used approximately $117.0 million of the net proceeds from the IPO. There has been no material change in the planned use of IPO proceeds from that described in the final prospectus related to our IPO filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act of 1933, as amended, on February 12, 2021.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

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 consolidated financial statements and related notes thereto appearing elsewhere in this Annual Report on Form 10-K, or Annual Report. Some of the information contained in this discussion and analysis includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the section entitled "Risk Factors," our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Please also see the section entitled "Cautionary Note Regarding Forward-Looking Statements and Industry Data" of this Annual Report.

Overview

We are a clinical-stage biotechnology company dedicated to discovering and developing transformative treatments for hearing and balance disorders, one of the largest areas of unmet need in medicine. We aim to restore and improve hearing and balance through the restoration and regeneration of functional hair cells and non-sensory support cells within the inner ear. We have built a proprietary platform that integrates single-cell genomics and bioinformatics analyses, precision gene therapy technologies and our expertise in inner ear biology. We are leveraging our platform to advance our pipeline of clinical and preclinical gene therapy programs that are designed to selectively replace genes for the treatment of congenital, monogenic hearing loss and to regenerate inner ear hair cells for the treatment of acquired hearing and balance disorders. We are developing our lead gene therapy product candidate, DB-OTO, to provide durable, high quality, physiological hearing to individuals with profound, congenital hearing loss caused by mutations of the otoferlin, or OTOF, gene. In addition to DB-OTO, we are advancing AAV.103 to restore hearing in individuals with mutations in the gap junction beta-2, or GJB2, gene, AAV.104 to restore hearing in individuals with mutations in the stereocilin, or STRC, gene and AAV.105 to restore hearing in individuals with another single gene mutation. We also have gene therapy programs to convert supporting cells, the cells adjacent to hair cells, into either cochlear or vestibular hair cells in order to restore hearing or balance function. In addition to our gene therapy programs, we are developing DB-020 for the prevention of cisplatin-induced hearing loss. We ceased enrolling patients in our Phase 1b clinical trial of DB-020, subsequent to announcing the positive results from the interim analysis from the first 19 patients enrolled in the trial. We are in the safety follow-up portion of the clinical trial, which we anticipate to be completed in the first half of 2023.

Since inception, we have devoted substantially all of our resources to organizing and staffing, business planning, raising capital, establishing our intellectual property portfolio and performing research and development of our product candidates, programs and platform.

On February 5, 2021, we issued and sold 15,870,209 shares of our Series D convertible preferred stock for $27.4 million of aggregate cash proceeds, net of issuance costs. On February 17, 2021, we completed an initial public offering, or IPO, of our common stock in which we issued and sold 7,062,000 shares of our common stock at a public offering price of $18.00 per share, and on February 24, 2021, we issued and sold an additional 600,000 shares of common stock pursuant to the underwriters' partial exercise of their option to purchase additional shares of common stock, for aggregate net proceeds of $125.0 million. Upon the closing of our IPO, all of our outstanding shares of convertible preferred stock automatically converted into 16,662,011 shares of common stock. Subsequent to December 31, 2022, we issued and sold a total of 50,482 shares under the Sales Agreement for aggregate net proceeds of $0.2 million after deducting commissions payable by us.

To date, we have financed our operations primarily with proceeds from sales of our convertible preferred stock (including borrowings under convertible promissory notes, which converted into convertible preferred stock in 2015), payments received under our license and collaboration agreement with Regeneron Pharmaceuticals, Inc., or Regeneron, and from the sale of common stock in our IPO and from the sale of common stock under our "at-the-market offering" program. We have not generated any revenue from product sales, and do not expect to generate any revenue from product sales for at least the next several years. All of our programs are still in preclinical and early-stage clinical development. 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 product candidates, if approved. Since inception, we have incurred significant operating losses. Our net losses were $63.0 million and $51.8 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $277.5 million. We expect to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will increase if, and as, we:

- initiate and conduct our planned Phase 1/2 clinical trial of DB-OTO for the treatment of profound hearing loss caused by mutations of the OTOF gene;
- continue our current research programs and our preclinical development of AAV.103, AAV.104, AAV.105, our vestibular hair cell regeneration programs and our cochlear hair cell regeneration program and any product candidates that may arise from our current or future research programs;

- continue the clinical development of DB-020;
- advance additional product candidates into preclinical and clinical development;
- expand the capabilities of and invest in our platform;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- expand, maintain and protect our intellectual property portfolio;
- hire additional clinical, research, development, scientific, regulatory and quality control personnel;
- establish and maintain agreements with manufacturers for our product candidates; and
- add operational, legal, compliance, financial and management information systems and personnel, including personnel to support our research, product development and future commercialization efforts and support our operations as a public company.

In addition, as we progress toward marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution.

As a result, we will need substantial additional funding to support our continuing operations and pursue our strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings and other sources of capital, which may include collaborations with other companies or other strategic transactions. We may be unable to raise additional funds or enter into other collaborations, strategic alliances or licensing arrangements with third parties when needed or on favorable terms, or at all. If we are unable to raise additional funds through equity or debt financings or enter into such other agreements when needed, we may have to significantly delay, reduce or eliminate some or all of 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.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve profitability. Even if we are able to generate revenue from product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2022, we had cash, cash equivalents and available-for-sale securities of $104.6 million, which we believe will enable us to fund our operating expenses and capital expenditures requirements into the first half of 2024. Since our cash, cash equivalents and available-for-sale securities as of December 31, 2022 are not sufficient to fund our operations for at least twelve months from the date of issuance of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K, there is substantial doubt about our ability to continue as a going concern. Our future viability is dependent on our ability to raise additional capital to finance our operations. We expect to finance our operations through potential public or private equity financings, debt financings, collaboration agreements or other sources of capital. Our inability to raise capital as and when needed could have a negative impact on our financial condition and ability to pursue our business strategies. There can be no assurance that the current operating plan will be achieved or that additional funding will be available on terms acceptable to us, or at all. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we anticipate. See Note 1 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for additional information on our assessment.

Macroeconomic and Geopolitical Impacts on Our Business

The worldwide COVID-19 pandemic has affected and may affect in the future our ability to initiate and complete preclinical studies, initiate and conduct clinical trials and engage in regulatory activities and may cause other adverse effects on our business, results of operations, financial condition and prospects. In addition, the pandemic has caused substantial disruption to global supply chains and may adversely impact economies worldwide, both of which could adversely affect our business, operations and ability to raise funds to support our operations.

We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business. The extent of the impact of COVID-19 on us will depend on the length and severity of the pandemic, including the extent there is any resurgence of the COVID-19 virus or any variant strains of the virus, the availability and effectiveness of vaccines and the

impact of the foregoing on our preclinical studies, current and planned clinical trials, employees and vendors, which is uncertain and cannot be predicted. The pandemic has the potential to adversely affect our business, financial condition, results of operations and prospects.

In addition, U.S. and global financial markets have experienced disruption due to various macroeconomic and geopolitical events. These include, but are not limited to, rising inflation, rising interest rates, the risk of a recession and other ongoing global conflicts. For example, on Friday, March 10, 2023, the Federal Deposit Insurance Corporation, or FDIC, announced that Silicon Valley Bank, or SVB, was closed and that the FDIC was appointed as receiver, and on March 12, 2023, the FDIC announced that Signature Bank was closed and that the FDIC was appointed as receiver. We cannot predict at this time to what extent our or our collaborators, employees, suppliers, contract manufacturers and/or vendors could be negatively impacted by these and other macroeconomic and geopolitical events.

License and Collaboration Agreement with Regeneron

In November 2017, we entered into a license and collaboration agreement with Regeneron, or the Regeneron Agreement. The Regeneron Agreement had an original research term of five years and granted Regeneron the right to extend the research term for up to two years in one-year intervals. In November 2021, Regeneron exercised its right to extend the research term and extended the research term by one year to November 2023. The Regeneron Agreement is focused on the discovery and development of new potential therapies directed to a set of defined collaboration targets. We are currently developing DB-OTO, AAV.103 and AAV.104 in collaboration with Regeneron under the Regeneron Agreement. In October 2020, we entered into an amendment to the Regeneron Agreement pursuant to which, among other things, ATOH1, the target of our DB-ATO program, was removed as a collaboration target and the terms and plans for the DB-OTO and AAV.103 programs were modified. We issued 10,000,000 shares of our Series C convertible preferred stock to Regeneron in consideration for its entry into the amendment. In February 2023, we further amended the Regeneron Agreement to provide for accelerated development milestone payments by Regeneron to us for clinical development milestones for DB-OTO and pre-IND milestones for AAV.103.

Pursuant to the Regeneron Agreement, Regeneron paid us an upfront fee of $25.0 million and purchased 12,500,000 shares of our Series B convertible preferred stock at a price per share of $2.00. In November 2021, Regeneron exercised its right to extend the research term for one-year to November 15, 2023 and paid us an extension fee of $10.0 million in the fourth quarter of 2022. On a collaboration-product-by-collaboration-product basis, upon achievement of pre-defined milestones which begin at initiation of manufacturing to support Good Laboratory Practices, or GLP toxicology studies and conclude at initiation of a Phase 2 clinical trial, Regeneron is obligated to pay us milestone payments of up to $35.5 million in aggregate if the collaboration product is a biologic or up to $33.5 million in aggregate if the collaboration product is a small molecule, which is intended to reflect approximately half of the total cost needed to achieve the next milestone. From and after the initiation of a registration-enabling trial, unless Regeneron decides to opt-out, we have agreed to split development and regulatory costs with Regeneron on an equal basis through the registration-enabling trials. Through December 31, 2022, we had received an aggregate of $5.5 million in milestone payments from Regeneron pursuant to the collaboration.

Under the Regeneron Agreement, we are required to pay Regeneron tiered royalties on the worldwide net sales of collaboration products at percentages which range from mid-single digit to mid-thirties, with the exact royalty rate depending on the extent to which Regeneron shared in the funding of the collaboration product, the level of net sales of the collaboration product, the nature of any intellectual property contributed by Regeneron included in the collaboration product and whether the product is sold inside or outside the field. In the case of collaboration products for which Regeneron does not opt-out, our obligation to pay tiered royalties on the worldwide net sales ranges from percentages in the mid-twenties to mid-thirties. In the case of collaboration products for which Regeneron opts-out, our obligation to pay tiered royalties on the worldwide net sales ranges from percentages in the mid-single digits to mid-twenties. Our obligation to make royalty payments to Regeneron on account of worldwide net sales of collaboration products continues so long as we, our affiliates, licensees or sublicensees sell collaboration products. To date, we have not made any royalty or other payments to Regeneron under the Regeneron Agreement.

Pursuant to the first amendment to the Regeneron Agreement, Regeneron agreed to pay us $0.3 million to fund our ongoing research program and $0.5 million to help secure the services of a contract development and manufacturing organization, or CDMO. The $0.5 million payment was creditable against the milestone associated with the initiation of manufacturing to support GLP toxicology studies of DB-OTO. Additionally, Regeneron agreed to reimburse us for up to $10.5 million of third-party costs related to the GLP toxicology studies of DB-OTO as such costs are incurred, and we agreed that the aggregate potential milestone payments for DB-OTO would be reduced by $15.0 million. In addition, notwithstanding its removal from the collaboration, for DB-ATO, we agreed to pay to Regeneron a royalty calculated as a low-to mid-single digit percentage of net sales of DB-ATO, on a country-by-country basis, until the latest of the expiration of

the last patent covering DB-ATO in such country, the expiration of all applicable regulatory exclusivities for DB-ATO in such country and the tenth anniversary of the first commercial sale of DB-ATO in such country.

Because we consider Regeneron a collaborative partner that is subject to the significant risks and rewards under the Regeneron Agreement, we have accounted for the Regeneron Agreement under FASB ASC Topic 808, *Collaborative Arrangements*, or ASC 808. Under ASC 808, we view all consideration received from Regeneron as reimbursement of our costs under the Regeneron Agreement. These costs are accounted for as research and development expenses in our consolidated statements of operations and comprehensive loss. As such, we are recognizing total consideration of $46.9 million over the research term as a reduction to research and development expenses (contra-research and development expense) in our consolidated statements of operations and comprehensive loss based on our progress toward completion of our research activities under the research plan. The $46.9 million is comprised of the $25.0 million upfront payment, the additional payment of $0.3 million received from Regeneron pursuant to the first amendment, the reimbursement of $10.5 million of third-party costs related to the GLP toxicology studies of DB-OTO, the $5.5 million of cumulative milestone payments received, and the $10.0 million extension payment paid in the fourth quarter of 2022, net of the $4.4 million in fair value of the Series C convertible preferred stock issued to Regeneron. Any future milestone payments will be included in the measurement of contra-research and development expense if and when achieved. We recognized $8.4 million and $11.0 million as contra-research and development expenses during the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had no unbilled accounts receivable due from Regeneron, and as of December 31, 2021, we had $11.4 million of unbilled accounts receivable due from Regeneron, that we collected during the year ended December 31, 2022. As of December 31, 2022 and 2021, we had total deferred collaboration liabilities of $16.1 million and $24.5 million on our consolidated balance sheet, respectively. As of December 31, 2022 and 2021 we had $9.4 million and $8.1 million of current deferred collaboration liabilities, respectively, and $6.8 million and $16.4 million of long-term deferred collaboration liabilities, respectively. See Note 13 to our consolidated financial statements appearing elsewhere in this Annual Report.

Financial Operations Overview

Revenue

We have not generated any revenue since inception and do not expect to generate any revenue from the sale of products for at least the next several years. If our development efforts for our current or future product candidates are successful and result in marketing approval or if we enter into collaboration or license agreements with third parties, we may generate revenue in the future from product sales or payments from third-party collaborators or licensors.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities and development of our programs and product candidates. These expenses include:

- personnel-related expenses, including salaries, benefits and stock-based compensation expense for employees engaged in research and development functions;
- expenses incurred under agreements with third parties, such as consultants and investigative sites that conduct our preclinical studies and clinical trials and in-licensing arrangements;
- costs incurred to maintain compliance with regulatory requirements;
- costs incurred with third-party CDMOs to acquire, develop and manufacture materials for preclinical and clinical studies;
- costs associated with our technology and development of our intellectual property portfolio;
- expenses incurred for the procurement of materials, laboratory supplies and non-capital equipment used in the research and development process; and
- depreciation, amortization and other direct and allocated expenses, including rent, insurance and other operating costs, incurred as a result of our research and development activities.

We use our employee and infrastructure resources for the advancement of our platform and for discovering and developing programs and product candidates. We track direct research and development costs, consisting primarily of external costs, such as fees paid to CDMOs, CROs and consultants in connection with our preclinical studies, clinical trials and experiments by program after a development candidate has been identified. Due to the number of ongoing programs and our ability to use resources across several projects, personnel-related expenses and indirect or shared operating costs incurred for our research and development programs are not recorded or maintained on a program-by-program basis, nor are our external program costs incurred for our programs prior to the identification of a development candidate for such program.

The following table reflects our research and development expense, including direct program-specific expense summarized by program, personnel-related expenses and indirect or shared operating costs recognized during each period presented (in thousands):

	Year Ended December 31,	
	2022	2021
DB-OTO	$ 19,252	$ 18,007
DB-020	2,232	1,831
Personnel-related (including stock-based compensation)	13,903	9,425
Regeneron Agreement contra-expense	(8,402)	(10,960)
Other indirect research and development expenses	13,345	11,544
Total research and development expenses	$ 40,330	$ 29,847

Consideration we receive under the Regeneron Agreement is being recognized as a reduction to research and development expense (contra-research and development expense) in our consolidated statements of operations and comprehensive loss based on our progress towards completion of our research activities under the research plan for the collaboration.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase for the foreseeable future as we advance our programs and product candidates into and through the development phase, and as we continue to develop additional product candidates. We also expect our discovery research efforts and our related personnel costs will increase and, as a result, we expect our research and development expenses will increase above historical levels. In addition, we may incur additional expenses related to milestone and royalty payments payable to third parties with whom we may enter into license, acquisition and option agreements to acquire the rights to future product candidates.

At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the development of, and obtain regulatory approval for, any of our product candidates or programs. This is due to the numerous risks and uncertainties associated with drug development, including the uncertainty of:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- our ability to successfully complete clinical trials with safety, potency and purity profiles that are satisfactory to the FDA or any comparable foreign regulatory authority;
- our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize, our product candidates;
- our ability to hire and retain key research and development personnel;
- our successful enrollment in and completion of clinical trials;
- the costs associated with the development of any additional product candidates we develop or acquire through collaborations;
- our ability to establish and maintain agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if our product candidates are approved;
- the terms and timing of any collaboration, license or other arrangement, including the terms and timing of any milestone payments thereunder;

- our ability to obtain and maintain patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates if and when approved;
- our receipt of marketing approvals from applicable regulatory authorities;
- our ability to commercialize products, if and when approved, whether alone or in collaboration with others;
- the continued acceptable safety profiles of the product candidates following approval; and
- the effects of the COVID-19 pandemic on our research and development employees, contractors and those who may participate in our studies.

A change in any of these variables with respect to the progress of any of our product candidates would significantly change the costs, timing and viability associated with the development of that product candidate. We may never succeed in obtaining regulatory approval for any product candidate we may develop.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel-related costs, including salaries, benefits and stock-based compensation, for personnel in our executive, finance, legal, business development, human resources and administrative functions. General and administrative expenses also include legal fees relating to corporate matters and costs to secure and defend our intellectual property; professional fees for accounting, auditing, tax, human resources and administrative consulting services; insurance costs; administrative travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for office rent and other operating costs. General and administrative expenses also reflect sublease income that is used to offset the cost for office rent and other operating costs. These costs relate to the operation of the business, unrelated to the research and development function, or any individual program.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support the expected growth in our research and development activities and the potential commercialization of our product candidates. We also expect to continue to incur significant expenses associated with being a public company, including costs for accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance costs and investor and public relations costs. We also expect to incur additional intellectual property-related expenses as we file patent applications to protect innovations arising from our research and development activities.

Interest Income

Interest income consists of interest income earned from our cash, cash equivalents and available-for-sale securities.

Other Income, net

Other income, net for the year ended December 31, 2021 primarily consisted of income received from the sale of consumables and other supplies to third parties that we were not using and were not planning to use in the future. There was no other income, net recognized for the year ended December 31, 2022.

Income Taxes

Since our inception, we have not recorded any U.S. federal, foreign, or state income tax benefits for the net losses we have incurred in each year or for our earned research and development tax credits, as it is more likely-than-not that these benefits will not be realized. We have U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards to offset future taxable income. We have recognized a reserve for a foreign uncertain tax position and recorded a foreign tax provision related to our Australian subsidiary.

Income taxes are determined at the applicable tax rates adjusted for non-deductible expenses, research and development tax credits and other permanent differences. Our income tax provision may be significantly affected by changes to our estimates.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for each period presented (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Operating expenses:			
Research and development	$ 40,330	$ 29,847	$ 10,483
General and administrative	23,627	20,384	3,243
Total operating expenses	63,957	50,231	13,726
Loss from operations	(63,957)	(50,231)	(13,726)
Other income:			
Interest income	1,192	193	999
Other income	—	12	(12)
Total other income, net	1,192	205	987
Net loss before provision for income taxes	(62,765)	(50,026)	(12,739)
Provision for income taxes	(240)	(1,797)	1,557
Net loss	$ (63,005)	$ (51,823)	$ (11,182)

Research and Development Expenses

The following table summarizes our research and development expenses for each period presented (in thousands):

	Year Ended December 31,		
	2022	2021	Change
DB-OTO	$ 19,252	$ 18,007	$ 1,245
DB-020	2,232	1,831	401
Personnel-related (including stock-based compensation)	13,903	9,425	4,478
Regeneron Agreement contra-expense	(8,402)	(10,960)	2,558
Other indirect research and development expenses	13,345	11,544	1,801
Total research and development expenses	$ 40,330	$ 29,847	$ 10,483

Research and development expenses for the year ended December 31, 2022 were $40.3 million, compared to $29.8 million for the year ended December 31, 2021. The increase of $10.5 million was primarily attributable to the following:

- $1.2 million increase in expenses incurred to advance DB-OTO, primarily attributable to an increase of $2.8 million of clinical and translational research costs to support our upcoming Phase 1/2 clinical trial of DB-OTO, $1.7 million for preclinical and IND-enabling costs, and an increase of $1.0 million for external support and additional costs to support the Company's regulatory submissions; all of which was partially offset by a decrease of $4.2 million in external manufacturing costs reflecting IND-enabling activities incurred during the year ended December 31, 2021;
- $0.4 million increase in expenses incurred for our DB-020 program, primarily attributable to clinical trial costs related to enrollment in our Phase 1b clinical trial of DB-020 and additional external support related to the positive interim analysis results reported in June 2022;
- $4.5 million increase in personnel-related costs due to increased headcount and wages within the research and development function in 2022, including $0.2 million of increased stock-based compensation expense;
- $2.6 million decrease in contra-research and development expenses recognized under the Regeneron Agreement, driven primarily by the completion of a performance obligation associated with the clearance of the IND for DB-OTO during the year ended December 31, 2022; and
- $1.8 million increase in other indirect research and development expenses, driven primarily by a $1.6 million increase in preclinical expenses relating to internal and external research and discovery efforts for our preclinical programs, as well as a $0.2 million increase in facility and infrastructure related costs to support our research and development efforts.

General and Administrative Expense

General and administrative expenses for the year ended December 31, 2022 were $23.6 million, compared to $20.4 million for the year ended December 31, 2021. The increase of $3.2 million was primarily attributable to the following:

- $2.5 million increase in professional fees, driven primarily by expenses related to external legal services, as well as consulting, accounting advisory and audit services;
- $2.0 million increase in personnel-related costs due to increased headcount and wages within the general and administrative function, including $0.2 million of increased stock-based compensation expense;
- $0.6 million increase in other corporate infrastructure costs including insurance, information technology costs, and other costs associated with operating as a public company; and
- $1.9 million decrease in facility-related expenses, primarily due to additional sublease income recognized during the year ended December 31, 2022.

Interest Income

The increase in interest income for the year ended December 31, 2022 compared to the year ended December 31, 2021 was primarily attributable to an increase in interest rates and higher yields from our investments in cash equivalents and available-for-sale securities.

Other Income, net

Other income, net for the year ended December 31, 2021 primarily consisted of income received from the sale of consumables and other supplies to third parties that we were not using and were not planning to use in the future. There was no other income, net recognized for the year ended December 31, 2022.

Provision for Income Taxes

The provision for income taxes for the year ended December 31, 2022 was due to the recognition of $0.2 million related to a foreign tax provision for our Australian subsidiary and interest expense related to a previously established foreign uncertain tax position. The provision for income taxes for the year ended December 31, 2021, was due to the recognition of an income tax expense of $1.8 million related to an uncertain tax position in a foreign jurisdiction and a foreign tax provision for our Australian subsidiary.

Liquidity and Capital Resources

Sources of Liquidity and Capital

Since our inception, we have incurred significant operating losses and negative cash flows from operations. We have not yet commercialized any of our product candidates, which are in various phases of preclinical and clinical development, and we do not expect to generate revenue from sales of any products for several years, if at all. Through December 31, 2022, we funded our operations primarily from net proceeds of $219.5 million from the issuance and sale of our convertible preferred stock, $51.3 million from the Regeneron Agreement and $125.0 million of net proceeds from the issuance and sale of our common stock in our IPO.

In March 2022, we filed a universal shelf registration statement on Form S-3 to register for sale from time to time up to $200.0 million of common stock, preferred stock, debt securities, warrants and/or units in one or more offerings. Further, in March 2022, we entered into an Open Market Sale Agreement℠, or the Sales Agreement, with Jefferies LLC, or Jefferies, pursuant to which, from time to time, we may offer and sell shares of our common stock. Sales of common stock through Jefferies may be made by any method that is deemed an "at-the-market" offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. Jefferies is entitled to compensation at a rate equal to 3.0% of the gross proceeds from any shares of common stock sold under the Sales Agreement. In August 2022, we filed a prospectus supplement under our universal shelf registration for the offer and sale of shares of our common stock having an aggregate offering price up to $50.0 million pursuant to the Sales Agreement. As of December 31, 2022, we had not sold any shares of common stock pursuant to the Sales Agreement. Subsequent to December 31, 2022, we issued and sold a total of 50,482 shares under the Sales Agreement for aggregate net proceeds of $0.2 million after deducting commissions payable by us.

Cash Flows

The following table provides information regarding our cash flows for each period presented (in thousands):

	Year Ended December 31,	
	2022	2021
Net cash provided by (used in):		
Operating activities	$ (56,898)	$ (43,150)
Investing activities	55,097	(100,995)
Financing activities	(213)	152,510
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (2,014)	$ 8,365

Operating Activities

Our cash flows from operating activities are greatly influenced by our use of cash for operating expenses and working capital requirements to support the business. We have historically experienced negative cash flows from operating activities as we invested in developing our pipeline, platform, drug discovery efforts and related infrastructure. The cash used in operating activities resulted primarily from our net losses adjusted for non-cash charges, which are generally attributable to stock-based compensation, depreciation and amortization and accretion of discounts on available-for-sale securities, as well as changes in components of operating assets and liabilities, which are generally attributable to increased expenses, timing of vendor payments and performance under the Regeneron Agreement.

During the year ended December 31, 2022, net cash used in operating activities of $56.9 million was primarily due to our net loss of $63.0 million and changes in operating assets and liabilities of $0.6 million, partially offset by net non-cash expenses of $6.7 million.

During the year ended December 31, 2021, net cash used in operating activities of $43.2 million was primarily due to our net loss of $51.8 million, partially offset by net non-cash expenses of $5.2 million and changes in operating assets and liabilities of $3.5 million.

Investing Activities

During the year ended December 31, 2022, net cash provided by investing activities of $55.1 million was primarily due to proceeds from the maturities of available-for-sale securities of $153.1 million, partially offset by purchases of available-for-sale securities of $97.5 million and purchases of property and equipment of $0.5 million.

During the year ended December 31, 2021, net cash used in investing activities of $101.0 million was primarily due to purchases of available-for-sale securities of $197.5 million and purchases of property and equipment of $0.8 million, partially offset by maturities of available-for-sale securities of $97.1 million and proceeds from sale of property and equipment of $0.1 million.

Financing Activities

During the year ended December 31, 2022, net cash used in financing activities of $0.2 million consisted of principal payments on our finance lease liability.

During the year ended December 31, 2021, net cash provided by financing activities of $152.5 million consisted primarily of proceeds from the issuance and sale of common stock, net of cash paid for offering costs, in connection with our IPO of $125.0 million, and proceeds from the issuance and sale of our Series D convertible preferred stock of $27.4 million, net of cash paid for offering costs.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing research and development activities, particularly as we advance the preclinical activities and clinical trials of our product candidates. In addition, we expect to continue to incur increased costs associated with operating as a public company. As a result, we expect to incur substantial operating losses and negative operating cash flows for the foreseeable future.

As of December 31, 2022, we had cash, cash equivalents and available-for-sale securities of $104.6 million. Subsequent to December 31, 2022, we issued and sold a total of 50,482 shares under the Sales Agreement for aggregate net proceeds of $0.2 million after deducting commissions payable by us. Based on our current operating plan, we believe that our cash, cash equivalents and available-for-sale securities as of December 31, 2022 will enable us to fund our operating

expenses and capital expenditure requirements into the first half of 2024. We have incurred recurring losses since our inception, including a net loss of $63.0 million for the year ended December 31, 2022. In addition, as of December 31, 2022, we had an accumulated deficit of $277.5 million. Our future viability is dependent on our ability to raise additional capital to finance our operations. We expect to finance our operations through potential public or private equity financings, debt financings, collaboration agreements or other sources of capital. Our inability to raise capital as and when needed could have a negative impact on our financial condition and ability to pursue our business strategies. There can be no assurance that the current operating plan will be achieved or that additional funding will be available on terms acceptable to us, or at all. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we anticipate.

Because of the numerous risks and uncertainties associated with product development, and because the extent to which we may enter into collaborations with third parties for the development of our product candidates is unknown, we may incorrectly estimate the timing and amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates. Our funding requirements and timing and amount of our operating expenditures will depend on many factors, including, but not limited to:

- the progress, costs and results of our planned Phase 1/2 clinical trial of DB-OTO and any future clinical development of DB-OTO;
- the approach we determine for the advancement of DB-020, including further potential clinical development;
- the scope, progress, costs and results of preclinical and clinical development for our other product candidates and programs, including AAV.103, AAV.104, AAV.105, our vestibular hair cell regeneration program and our cochlear hair cell regeneration program;
- the number of, and development requirements for, other product candidates that we may identify and develop;
- the scope, costs, timing and outcome of regulatory review of our product candidates;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the success of our collaboration with Regeneron;
- the payment or receipt of milestones and of other collaboration-based revenues, if any;
- our ability to establish and maintain additional strategic collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the amount and timing of revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights and defending any intellectual property-related claims;
- the extent to which we may acquire or in-license other products, product candidates and technologies;
- the impacts of the COVID-19 pandemic;
- the impact of continued increases in inflation rates or interest rates;
- the ability to receive additional non-dilutive funding, including grants from organizations and foundations; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for several years, if ever. Accordingly, we will need to obtain substantial additional funds to achieve our business objectives.

Our expectation with respect to our ability to fund current planned operations is based on estimates that are subject to risks and uncertainties. Our operating plan may change as a result of many factors currently unknown to management and there can be no assurance that the current operating plan will be achieved in the time frame anticipated by us, and we may need to seek additional funds sooner than planned.

Adequate additional funds may not be available to us on acceptable terms, or at all. We do not have any committed external source of funds, other than amounts we are entitled to under the Regeneron Agreement. Market volatility or other factors could also adversely impact our ability to access capital as and when needed. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interests of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of holders of our common stock. Additional debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could potentially dilute the ownership interests of holders of our common stock.

We may be unable to raise additional funds or enter into other collaborations, strategic alliances or licensing arrangements with third parties when needed on favorable terms, or at all. If we are unable to raise additional funds through equity or debt financings or enter into such agreements when needed, we may have to significantly delay, reduce or eliminate some or all of 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 or on terms that may not be favorable to us.

We have concluded that the above circumstance raises substantial doubt about our ability to continue as a going concern. See Note 1 of our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for additional information on our assessment.

Material Cash Requirements

The following discussion summarizes our material cash requirements from contractual and other obligations.

We lease and sublease, as sublessee, office and laboratory space at 1325 Boylston Street in Boston, Massachusetts. Our operating lease and sublease expire in June 2027 and January 2027, respectively. Our lease and sublease both contain rent escalation provisions over their respective lease terms, and we are obligated to pay our ratable portions of operating expenses and taxes. Our operating lease includes the option to extend the term for a period of five years at the then-market rental rate. Our lease and sublease are secured by letters of credit totaling $0.9 million. During the year ended December 31, 2022, we were obligated to make base rent payments totaling $3.7 million, excluding our ratable portions of operating expenses and taxes. Base rent will be subject to annual rent increases between 2% to 3%, thereafter. We are obligated to make cumulative rent payments of $16.7 million over the remaining lease and sublease terms, excluding operating expenses, taxes and the extension term.

In January 2022, we entered into a sublease agreement to sublease an additional portion of our existing office space to a third-party in order to offset a portion of our rent obligations. The lease term commenced in February 2022 with an original term of six months and has been extended through May 2023 for a base rent of $0.1 million per month. There is no rent escalation under the sublease and there is no further option to extend the term of the sublease agreement.

In August 2019, we entered into a license agreement with The Curators of the University of Missouri, or the University of Missouri, which was amended in February 2021 and May 2022, relating to certain patent rights. Pursuant to the agreement, we agreed to pay a low single-digit royalty on annual net sales of licensed products sold and are obligated to make milestone payments on a licensed-product-by-licensed-product basis totaling up to $0.8 million in the aggregate upon the achievement of certain development and regulatory milestones and up to $13.1 million in the aggregate upon the achievement of certain commercial sales milestones. During the year ended December 31, 2022, we achieved and paid less than $0.1 million with respect to a regulatory milestone related to our submission of an IND application for DB-OTO. We are also required to pay the University of Missouri a nominal annual license maintenance fee. We can terminate this agreement upon written notice at any time.

In October 2019, we entered into a license agreement with The Regents of the University of California, or UCSF, relating to certain patent rights. Pursuant to the agreement, we agreed to pay UCSF low single-digit royalties on annual net sales of licensed products and services and make contingent milestone payments totaling up to $0.5 million upon the achievement of certain regulatory milestones and up to $5.0 million upon the achievement of certain commercial sales milestones. No regulatory or commercial milestones have been achieved to date. We are also required to pay UCSF a nominal annual license maintenance fee. We can terminate this agreement upon written notice at any time.

In October 2020, we entered into a license agreement with the University of Florida Research Foundation, Incorporated, or UFRF, which was amended in June 2022, related to certain patent rights. Pursuant to the agreement, we have agreed to pay UFRF a low single-digit royalty on annual net sales of licensed products and make contingent milestone payments totaling up to $0.8 million in the aggregate upon the achievement of certain clinical and regulatory milestones and up to an additional $11.2 million in the aggregate upon the achievement of certain commercial sales milestones. No clinical, regulatory or commercial milestones have been achieved to date. We are also required to pay UFRF a nominal annual license maintenance fee. We can terminate this agreement upon written notice at any time.

We have agreements with certain vendors for various services, including services related to preclinical and clinical operations and support, for which we are not contractually able to terminate for convenience and avoid any and all future obligations to the vendors. Certain agreements provide for termination rights subject to termination fees or wind down costs. Under such agreements, we are contractually obligated to make certain payments to vendors to reimburse them for their

unrecoverable outlays incurred prior to cancellation. The exact amounts of such obligations are dependent on the timing of termination and the exact terms of the relevant agreement and cannot be reasonably estimated.

In addition, we enter into standard indemnification agreements and/or indemnification sections in other agreements in the ordinary course of business. Pursuant to these agreements, we agree to indemnify, hold harmless and reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally our business partners. The term of these indemnification agreements is generally perpetual upon execution of the agreement. The maximum potential amount of future payments we could be required to make under these indemnification agreements cannot be reasonably estimated.

Critical Accounting Estimates and Significant Judgments

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

We believe the following accounting estimates used in the preparation of our consolidated financial statements have the most significant level of estimation uncertainty and are reasonably likely to have a material impact on our financial condition and results of operations. For a more detailed description of our significant accounting policies, see Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report.

Collaboration Agreements

While we account for the Regeneron Agreement in accordance with ASC 808, *Collaborative Arrangements*, we analogize to the guidance under FASB ASC Topic 606, *Revenue with contracts from customers,* to measure progress under the collaboration over time. We measure progress using a proportional performance measure based on actual research and development costs incurred relative to total estimated research and development costs to be incurred by us under the Regeneron Agreement. We account for the consideration we receive under the Regeneron Agreement as a reduction to research and development expense (contra-research and development expense) in our consolidated statements of operations and comprehensive loss based on our progress towards completion of our research activities under the research plan. Actual costs incurred are discussed in more detail below. The unrecognized portion of consideration received under the Regeneron Agreement is recorded as a deferred collaboration liability in our consolidated balance sheets.

The critical estimate in measuring such progress is the estimation of the total costs to complete our remaining obligations under the Regeneron Agreement. This includes a number of estimates and assumptions which contemplate both objective and subjective factors. Primary inputs to the estimate to complete our remaining performance obligations include the estimated internal personnel costs and third-party costs to support research and development activities through IND acceptance of multiple potential targets. Following IND acceptance, the same inputs are utilized to estimate the performance obligations for the target candidates' potential clinical trials. We forecast personnel costs based on a fully burdened full-time equivalent, or FTE, rate and the expected FTE required as the research plan progresses. This assumption considers our contractual minimum diligence effort measured based on a minimum number of FTE, actual FTE's incurred and trends therein that may be indicative of future effort, and forecasted changes in FTE based on the requirements under the research plan as well as any anticipated changes in headcount we expect to experience. We forecast third-party costs to support research and development activities based on the requirements under the research plan, historical experience and negotiated rates with vendors. Finally, we forecast third-party costs related to IND-enabling studies and clinical trials based on historical experience and estimates directly from third-party vendors.

Our estimates may vary relative to actual costs incurred for various reasons including number of targets being pursued, changes in scope, feedback from regulators, developments in the science over the term of the research plan and changes in costs for supplies, consumables and other materials needed for the collaboration. We actively monitor these estimates relative to actual costs incurred and update our forecasts when and as necessary. These variances represent changes in estimate and may result in material changes in recognition of contra-research and development expense over the term of the collaboration.

Research and Development Expenses and Related Accruals

Research and development expenses are comprised of costs incurred in performing research and development activities, including salaries, stock-based compensation and benefits, laboratory supplies, depreciation on and maintenance of research equipment, manufacturing expenses and external costs of outside vendors engaged to conduct preclinical and clinical development activities and the allocable portions of facility costs, such as rent, utilities, repairs and maintenance, depreciation, and general support services. Research and development expenses comprise a significant portion of our operating expenses and are a primary input in the measurement of progress under our license and collaboration agreement with Regeneron. All costs associated with research and development activities are expensed as incurred.

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of the estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- CROs and investigative sites in connection with performing research services, preclinical studies and clinical trials;
- vendors, including research laboratories, in connection with preclinical and clinical development activities; and
- vendors, including CDMOs, related to product manufacturing, development and distribution of preclinical studies and clinical trial materials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CDMOs and CROs that supply materials and conduct services. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or prepaid expense accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period.

Stock-Based Compensation

We issue stock-based awards to employees, directors and non-employees, generally in the form of stock options, restricted stock and restricted stock units. We measure all stock-based awards granted to employees, directors and non-employees as stock-based compensation expense at fair value in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation*.

We issue stock-based awards with service-based and performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated requisite service period of the award, which is generally the vesting term. Compensation expense related to awards to employees, directors and non-employees with performance-based vesting conditions is recognized when it becomes probable that the performance conditions will be met using the accelerated attribution method. We have no awards with market-based conditions. We recognize forfeitures as they occur.

We classify stock-based compensation expense in the consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's salary and related costs are classified or in which the award recipient's service payments are classified, as applicable.

We determine the fair value of restricted stock and restricted stock units in reference to the fair value of our common stock less any applicable purchase price. We estimate the fair value of our stock options granted using the Black-Scholes option pricing model, which requires inputs of subjective assumptions, including: (i) the expected volatility of our common stock, (ii) the expected term of the award, (iii) the risk-free interest rate, (iv) expected dividends and (v) the fair value of our

common stock. Due to the lack of a public market for the trading of our common stock prior to the completion of our IPO, and a lack of company-specific historical and implied volatility data, we base the estimate of expected volatility on the historical volatilities of a representative group of publicly traded guideline companies. For these analyses, we select companies with comparable characteristics and with historical share price information that approximates the expected term of the stock-based awards. We compute the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period that approximates the calculated expected term of our stock options. We will continue to apply this method until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We estimate the expected term of our stock options granted to employees and directors using the simplified method, whereby the expected term equals the average of the vesting term and the original contractual term of the option. We utilize this method as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The expected dividend yield is assumed to be zero as we have no current plans to pay any dividends on common stock. We have elected to use the expected term for stock options granted to non-employees, using the simplified method, as the basis for the expected term assumption. However, we may elect to use either the contractual term or the expected term for stock options granted to non-employees on an award-by-award basis.

Subsequent to the completion of our IPO, the fair value of the common stock underlying our stock-based awards is determined based on the trading price of our common stock on the Nasdaq Global Select Market on the date of grant.

Leases

Effective January 1, 2022, we adopted ASU No. 2016-02, Leases, or ASC 842, using the required modified retrospective approach and utilizing the effective date as its date of initial application. Prior periods are presented in accordance with previous guidance in FASB ASC Topic 840, Leases.

Upon adoption, we elected the package of practical expedients which allows entities to not reassess (i) whether an arrangement is or contains a lease, (ii) the classification of its leases, and (iii) the accounting for initial direct costs. Further, we elected, by class of underlying asset, the short-term lease exception for leases with terms of twelve months or less. In doing so, we did not recognize a lease liability or right-of-use asset on its balance sheets for such short-term leases. Finally, we elected, by class of underlying asset, the practical expedient to not separate lease and non-lease components.

Under ASC 842 we evaluate whether an arrangement is or contains a lease at contract inception. If a contract is or contains a lease, lease classification is determined at lease commencement, which represents the date at which the underlying asset is made available for use by us. Our lease terms are generally measured as the respective lease's noncancelable term and exclude any optional extension terms as we are not reasonably certain to exercise such options. We elected the short-term lease exemption and therefore do not recognize lease liabilities and right-of-use assets for lease arrangements with original lease terms of twelve months or less.

Lease liabilities represent our obligation to make lease payments under a lease arrangement. Lease liabilities are measured as the present value of fixed lease payments, discounted using an incremental borrowing rate, as interest rates implicit in our lease arrangements are generally not readily determinable. We elected the practical expedient to not separate lease and non-lease components for its real estate leases and therefore both are considered when determining the lease payments in a lease arrangement. Variable lease costs are expensed as incurred.

The incremental borrowing rate represents the interest rate at which we could borrow a fully collateralized amount equal to the lease payments, over a similar term, in a similar economic environment. We determine the incremental borrowing rate at lease commencement, generally using a synthetic credit rating based on our financial position and negative cash flows, factoring in adjustments for additional risks based on our economic condition, a survey of comparable companies with similar credit and financial profiles, as well as additional market risks, as may be applicable.

Right-of-use assets represent our right to use an underlying asset over its lease term. Right-of-use assets are initially measured as the associated lease liability, adjusted for prepaid rent and tenant incentives. We remeasure right-of-use assets and lease liabilities when a lease is modified, and the modification is not accounted for as a separate contract. A modification is accounted for as a separate contract if the modification grants us an additional right of use not included in the original lease agreement and the increase in lease payments is commensurate with the additional right of use. We assess our right-of-use assets for impairment consistent with its policy for impairment of long-lived assets held and used in operations.

Emerging Growth Company and Smaller Reporting Company Status

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, enacted in April 2012. As a result, we may take advantage of reduced reporting requirements that are otherwise applicable to public companies. In particular, 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. We have elected not to "opt out" of such extended transition period, which means that when a standard is issued or revised and it has different application dates for public or private companies, we can adopt the new or revised standard at the time private companies adopt the new or revised standard and may do so until such time that we either (1) irrevocably elect to "opt out" of such extended transition period or (2) no longer qualify as an emerging growth company.

We are also a "smaller reporting company" as defined in Rule 12b-2 under the Securities and Exchange Act of 1934, as amended. We may continue to be a smaller reporting company if either (i) the market value of our shares held by non-affiliates is less than $250 million or (ii) our annual revenue was less than $100 million during the most recently completed fiscal year and the market value of our shares held by non-affiliates is less than $700 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.

Recently Issued Accounting Pronouncements

We have reviewed all recently issued accounting pronouncements and have determined that, other than as disclosed in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report, such standards will not have a material impact on our financial statements or do not otherwise apply to our current operations.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest Rate Fluctuation Risk

We are exposed to market risk related to changes in interest rates. Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates. These changes affect our cash equivalents and available-for-sale securities, which consisted of cash and investments in money market funds, U.S. Agency discount notes, U.S. Treasury securities and U.S. Agency bonds as of December 31, 2022. However, because of the short-term nature of the instruments in our portfolio, an immediate change in market interest rates of 100 basis points would not have a material impact on the fair market value of our investment portfolio or on our financial position or results of operations.

Foreign Currency Fluctuation Risk

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we have contracted with and may continue to contract with foreign vendors. Our operations may be subject to fluctuations in foreign currency exchange rates in the future.

Inflation Fluctuation Risk

Inflation generally affects us by increasing our cost of labor and clinical trial costs. The global macroeconomic environment has experienced, and continues to experience, extraordinary challenges, including the highest rates of inflation in 40 years. These macroeconomic factors have contributed, and we expect will continue to contribute, to increased costs, among other concerns. We cannot predict how long these inflationary pressures will continue, or how they may change over time, but we expect to see continued impacts on the global economy, our industry and our company. During 2022, we experienced increases in interest income and costs across our business. If inflationary pressures continue to persist, they may continue to have an adverse impact on our consolidated financial position, results of operations and/or cash flows.

Item 8. Financial Statements and Supplementary Data.

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15, Exhibits and Financial Statement Schedules, of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

We maintain "disclosure controls and procedures" as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. In designing and evaluating our disclosure controls and procedures, 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 benefits of possible controls and procedures relative to their costs.

Our management, with the participation of our chief executive officer and chief financial officer, who serve as our principal executive officer and principal financial officer, respectively, has evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. Based on such evaluation, our chief executive officer and chief financial officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2022.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rule 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934). Our internal control over financial reporting is a process designed under the supervision of our principal executive officer and principal financial officer to provide reasonable assurance regarding the reliability of our financial reporting and the preparation of our financial statements for external purposes in accordance with generally accepted accounting principles. Management evaluated the effectiveness of our internal control over financial reporting as of December 31, 2022 using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control—Integrated Framework (the 2013 Framework). Management, under the supervision and with the participation of the principal executive officer and principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2022 and concluded that it was effective based on those criteria.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in Internal Control over Financial Reporting

There were no changes in internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the fiscal quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions That Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Except to the extent provided below, the information required by this Item 10 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders which we intend to file not later than 120 days after the end of our fiscal year ended December 31, 2022 and is incorporated herein by reference.

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of the code on our website, www.decibeltx.com. In addition, we intend to post on our website all disclosures that are required by law or Nasdaq listing standards concerning any amendments to, or waivers from, any provision of the code. Our website is not incorporated by reference into this Annual Report on Form 10-K and you should not consider any information contained in or accessible from our website to be a part of this Annual Report on Form 10-K.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this Item 13 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Our independent registered public accounting firm is Ernst & Young LLP, Boston, MA, PCAOB Auditor Firm ID: 42.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(1) For a list of the financial statements included herein, see Index to the Consolidated Financial Statements on page F-1 of this Annual Report on Form 10-K, which is incorporated into this Item by reference.

(2) Financial statement schedules have been omitted because they are either not required or not applicable or the information is included in the consolidated financial statements or the notes thereto.

(3) Exhibits

The exhibits filed as part of this Annual Report on Form 10-K are listed below.

Exhibit Number	Description
3.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, File No. 001-40030, filed February 17, 2021).
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K, File No. 001-40030, filed February 17, 2021).
4.1	Specimen Stock Certificate Evidencing Shares of Common Stock (incorporated by reference to Exhibit 4.1 to the Registrant's Registration Statement on Form S-1/A, File No. 333-252347, filed January 28, 2021).
4.2	Third Amended and Restated Investors' Rights Agreement, dated as of November 2, 2020, by and among the Registrant and the other parties thereto (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
4.3	Description of Securities Registered Under Section 12 of the Exchange Act (incorporated by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K, File No. 001-40030, filed March 29, 2021).
10.1#	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.2#	2015 Stock Incentive Plan, as amended (incorporated by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1/A, File No. 333-252347, filed February 8, 2021).
10.3#	Form of Restricted Stock Agreement under the 2015 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.4#	Form of Incentive Stock Option Agreement under the 2015 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.5#	Form of Nonstatutory Stock Option Agreement under the 2015 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.6#	2021 Stock Incentive Plan (incorporated by reference to Exhibit 10.6 to the Registrant's Registration Statement on Form S-1/A, File No. 333-252347, filed February 8, 2021).
10.7#	Form of Stock Option Agreement under the 2021 Stock Incentive Plan (incorporated by reference to Exhibit 10.7 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.8#	Form of Restricted Stock Unit Agreement under the 2021 Stock Incentive Plan (incorporated by reference to Exhibit 10.8 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.9#	Form of Restricted Stock Agreement under the 2021 Stock Incentive Plan (incorporated by reference to Exhibit 10.9 to the Registrant's Registration Statement on Form S-1/A, File No. 333-252347, filed February 8, 2021).

10.10#	Amended and Restated 2021 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q, File No. 001-40030, filed November 9, 2022).
10.11†	License and Collaboration Agreement, dated as of November 15, 2017, as amended, by and between Regeneron Pharmaceuticals, Inc. and the Registrant (incorporated by reference to Exhibit 10.11 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.12†	Standard Exclusive License Agreement, dated as of October 29, 2020, by and between the University of Florida Research Foundation, Incorporated and the Registrant (incorporated by reference to Exhibit 10.12 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.13†	License Agreement, dated as of October 3, 2019, by and between the Regents of the University of California and the Registrant (incorporated by reference to Exhibit 10.13 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.14†	Exclusive License Agreement, dated as of August 26, 2019, by and between the Curators of the University of Missouri and the Registrant (incorporated by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.15	Lease, dated as of July 20, 2016, as amended, by and between Boylston West LLC and the Registrant (incorporated by reference to Exhibit 10.15 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.16#	Consulting Agreement, dated as of November 11, 2019, as amended, by and between the Registrant and Laurence Reid, Ph.D. (incorporated by reference to Exhibit 10.16 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.17#	Offer of Employment, dated as of October 28, 2020, by and between the Registrant and Laurence Reid, Ph.D. (incorporated by reference to Exhibit 10.17 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.18#	Change in Control Agreement, dated as of November 2, 2020, by and between the Registrant and Laurence Reid, Ph.D. (incorporated by reference to Exhibit 10.18 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.19#	Offer of Employment, dated as of August 11, 2016, by and between the Registrant and John Lee (incorporated by reference to Exhibit 10.20 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.20#	Offer of Employment, dated as of September 9, 2020, by and between the Registrant and Elisabeth Leiderman, M.D. (incorporated by reference to Exhibit 10.21 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.21#	Offer of Employment, dated as of December 19, 2017, by and between the Registrant and Anna Trask (incorporated by reference to Exhibit 10.22 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.22#	Form of Severance and Change in Control Benefits Agreement (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, File No. 001-40030, filed August 10, 2021).
10.23#	Form of Change in Control Agreement (incorporated by reference to Exhibit 10.24 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.24	Sublease Agreement, dated June 20, 2019, by and between United HealthCare Services, Inc. and the Registrant (incorporated by reference to Exhibit 10.25 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021).
10.25†	First Amendment, dated as of February 3, 2021, to the License Agreement, dated as of August 26, 2019, by and between the Curators of the University of Missouri and the Registrant (incorporated by reference to Exhibit 10.27 to the Registrant's Registration Statement on Form S-1/A, File No. 333-252347, filed February 3, 2021).

10.26†	Second Amendment, dated as of May 3, 2022, to the License Agreement, dated as of August 26, 2019, by and between the Curators of the University of Missouri and the Registrant (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, File No. 001-40030, filed August 10, 2022).
10.27†	First Amendment, dated as of June 13, 2022, to the License Agreement, dated as of October 29, 2020, by and between the University of Florida Research Foundation, Incorporated and the Registrant (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q, File No. 001-40030, filed August 10, 2022).
10.28	Open Market Sale Agreement℠, dated as of March 18, 2022, by and between the Registrant and Jefferies LLC (incorporated by reference to Exhibit 1.2 to the Registrant's Registration Statement on Form S-3, File No. 333-263671, filed March 18, 2022).
10.29	Letter Agreement, dated September 9, 2022, by and between the Registrant and Elisabeth Leiderman incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, File No. 001-40030, filed November 9, 2022).
10.30*†	Second Amendment, dated February 6, 2023, to the License and Collaboration Agreement, dated as of November 15, 2017, as amended, by and between Regeneron Pharmaceuticals, Inc. and the Registrant
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 to the Registrant's Registration Statement on Form S-1, File No. 333-252347, filed January 22, 2021)
23.1*	Consent of Ernst & Young LLP, independent registered public accounting firm
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.
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.
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.
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.
101.INS*	Inline XBRL Instance Document
101.SCH*	Inline XBRL Schema Document
101.CAL*	Inline XBRL Calculation Linkbase Document
101.DEF*	Inline XBRL Definition Linkbase Document
101.LAB*	Inline XBRL Labels Linkbase Document
101.PRE*	Inline XBRL Presentation Linkbase Document
104	The cover page from the Company's Annual Report on Form 10-K for the year ended December 31, 2022, has been formatted in Inline XBRL.

* Filed herewith.

† Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

Management contract or compensatory plan or arrangement filed in response to Item 15(a)(3) of the Instructions to the Annual Report on Form 10-K.

Item 16. Form 10-K Summary

None

SIGNATURES

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

DECIBEL THERAPEUTICS, INC.

Date: March 14, 2023

By: /s/ Laurence Reid
Laurence Reid, Ph.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Laurence Reid Laurence Reid, Ph.D.	President and Chief Executive Officer, Director (Principal Executive Officer)	March 14, 2023
/s/ James Murphy James Murphy	Interim Chief Financial Officer (Principal Financial and Accounting Officer)	March 14, 2023
/s/ William H. Carson William H. Carson, M.D.	Director and Chairman of the Board	March 14, 2023
/s/ Kevin McLaughlin Kevin McLaughlin	Director	March 14, 2023
/s/ Neil Exter Neil Exter	Director	March 14, 2023
/s/ Alison Finger Alison Finger, MBA	Director	March 14, 2023
/s/ Saraswathy Nochur Saraswathy Nochur, Ph.D.	Director	March 14, 2023
/s/ Peter A. Thompson Peter A. Thompson, M.D.	Director	March 14, 2023

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Stockholders and Board of Directors of Decibel Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Decibel Therapeutics, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company has suffered recurring losses from operations, has limited financial resources, and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Adoption of ASU No. 2016-02

As discussed in Note 1 to the consolidated financial statements, the Company changed its method of accounting for Leases in 2022 due to the adoption of ASU No. 2016-02, Leases.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's 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/ Ernst & Young LLP

We have served as the Company's auditor since 2017.

Boston, Massachusetts
March 14, 2023

DECIBEL THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31,	
	2022	**2021**
Assets		
Current assets:		
Cash and cash equivalents	$ 34,607	$ 36,455
Available-for-sale securities	69,954	112,292
Accounts receivable from related party	—	11,402
Prepaid expenses and other current assets	3,469	4,042
Total current assets	108,030	164,191
Available-for-sale securities, long-term	—	13,547
Property and equipment, net	4,526	5,611
Right-of-use asset, operating	9,859	—
Right-of-use asset, finance	34	—
Other assets	924	1,128
Total assets	$ 123,373	$ 184,477
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,064	$ 4,012
Accrued expenses and other current liabilities	8,409	7,712
Deferred collaboration liability, current	9,383	8,118
Deferred rent and lease incentive obligation, current	—	696
Operating lease liability, current	3,567	—
Finance lease liability, current	19	—
Total current liabilities	22,442	20,538
Long-term liabilities:		
Deferred collaboration liability, long term	6,765	16,431
Deferred rent and lease incentive obligation, long term	—	4,208
Operating lease liability, long-term	10,467	—
Other long-term liabilities	1,906	1,611
Total liabilities	41,580	42,788
Commitments and contingencies (Note 8)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 5,000,000 shares authorized, no shares issued and outstanding at December 31, 2022 and December 31, 2021	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized, 24,964,502 shares issued and outstanding at December 31, 2022; 200,000,000 shares authorized, 24,964,520 shares issued and 24,951,983 shares outstanding at December 31, 2021	25	25
Additional paid-in capital	359,508	356,308
Accumulated other comprehensive loss	(223)	(132)
Accumulated deficit	(277,517)	(214,512)
Total stockholders' equity	81,793	141,689
Total liabilities and stockholders' equity	$ 123,373	$ 184,477

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

DECIBEL THERAPEUTICS, INC.
CONSOLIDATED 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	$ 40,330	$ 29,847
General and administrative	23,627	20,384
Total operating expenses	63,957	50,231
Loss from operations	(63,957)	(50,231)
Other income:		
Interest income	1,192	193
Other income, net	—	12
Total other income, net	1,192	205
Net loss before provision for income taxes	(62,765)	(50,026)
Provision for income taxes	(240)	(1,797)
Net loss	$ (63,005)	$ (51,823)
Cumulative dividends on convertible preferred stock	—	(2,309)
Net loss attributable to common stockholders	$ (63,005)	$ (54,132)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.52)	$ (2.49)
Weighted average shares of common stock outstanding, basic and diluted	24,960,008	21,733,960
Comprehensive loss:		
Net loss	$ (63,005)	$ (51,823)
Other comprehensive loss:		
Unrealized loss on available-for-sale securities, net of tax of $0	(91)	(131)
Total other comprehensive loss	(91)	(131)
Comprehensive loss	$ (63,096)	$ (51,954)

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

DECIBEL THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' (DEFICIT) EQUITY
(In thousands, except share data)

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Series C Convertible Preferred Stock		Series D Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2020	57,758,734	$ 16,176	12,500,000	$ 5,700	37,528,581	$ 16,759	31,740,554	$ 54,456	521,052	$ 1	$ 107,908	$ (1)	$ (162,689)	$ (54,781)
Issuance of common stock upon exercise of stock options	—	—	—	—	—	—	—	—	72,161	—	319	—	—	319
Vesting of restricted common stock	—	—	—	—	—	—	—	—	34,759	—	18	—	—	18
Stock-based compensation expense	—	—	—	—	—	—	—	—	—	—	2,817	—	—	2,817
Issuance of Series D convertible preferred stock	—	—	—	—	—	—	15,870,209	27,400	—	—	—	—	—	—
Conversion of convertible preferred stock into common stock upon completion of initial public offering	(57,758,734)	(16,176)	(12,500,000)	(5,700)	(37,528,581)	(16,759)	(47,610,763)	(81,856)	16,662,011	17	120,474	—	—	120,491
Issuance of common stock upon completion of initial public offering, net of commissions, underwriting discounts and offering costs of $13,137	—	—	—	—	—	—	—	—	7,662,000	7	124,772	—	—	124,779
Unrealized loss on available-for-sale securities	—	—	—	—	—	—	—	—	—	—	—	(131)	—	(131)
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	(51,823)	(51,823)
Balance at December 31, 2021	—	$ —	—	$ —	—	$ —	—	$ —	24,951,983	$ 25	$ 356,308	$ (132)	$ (214,512)	$ 141,689
Vesting of restricted common stock	—	—	—	—	—	—	—	—	12,519	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	—	—	—	—	—	—	3,200	—	—	3,200
Unrealized loss on available-for-sale securities	—	—	—	—	—	—	—	—	—	—	—	(91)	—	(91)
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	(63,005)	(63,005)
Balance at December 31, 2022	—	$ —	—	$ —	—	$ —	—	$ —	24,964,502	$ 25	$ 359,508	$ (223)	$ (277,517)	$ 81,793

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

DECIBEL THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,	
	2022	**2021**
Operating activities		
Net loss	$ (63,005)	$ (51,823)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	3,200	2,817
Depreciation	1,462	1,413
Non-cash lease expense	1,828	—
(Gain) loss on disposal of property and equipment	—	(35)
Amortization (accretion) of available-for-sale securities	235	987
Changes in operating assets and liabilities:		
Accounts receivable from related party	11,402	(10,165)
Prepaid expenses and other current assets	611	(1,761)
Accounts payable	(3,128)	1,881
Accrued expenses and other current liabilities	941	3,438
Deferred rent and lease incentive	—	(607)
Deferred collaboration liability	(8,401)	9,404
Operating lease liability	(2,355)	—
Other long-term liabilities	312	1,301
Net cash used in operating activities	(56,898)	(43,150)
Investing activities		
Purchases of available-for-sale securities	(97,513)	(197,457)
Proceeds from maturities of available-for-sale securities	153,073	97,068
Proceeds from sale of property and equipment	—	139
Purchases of property and equipment	(463)	(745)
Net cash provided by (used in) investing activities	55,097	(100,995)
Financing activities		
Proceeds from the issuance of Series D convertible preferred stock	—	27,400
Proceeds from issuance of common stock upon completion of initial public offering net of commissions and underwriting discounts	—	128,240
Payment of initial public offering costs	—	(3,255)
Proceeds from the exercise of stock options	—	319
Principal payments on finance lease liability	(213)	(193)
Repurchases of early exercised restricted stock	—	(1)
Net cash (used in) provided by financing activities	(213)	152,510
Net (decrease) increase in cash, cash equivalents and restricted cash	(2,014)	8,365
Cash, cash equivalents and restricted cash at beginning of period	37,583	29,218
Cash, cash equivalents and restricted cash at end of period	$ 35,569	$ 37,583
Supplemental cash flow information:		
Cash paid for interest for finance lease	$ 14	$ 34
Supplemental disclosure of non-cash activities:		
Operating lease right-of-use asset recognized upon adoption of ASC 842	$ 11,485	$ —
Property and equipment purchases in accounts payable and accrued expenses	$ 197	$ 46
Vesting of early exercised restricted stock	$ —	$ 18

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

1. Nature of the Business

Decibel Therapeutics, Inc. (the "Company") was formed on November 26, 2013. The Company is a clinical-stage biotechnology company dedicated to discovering and developing transformative treatments for hearing and balance disorders, one of the largest areas of unmet need in medicine. The Company aims to restore and improve hearing and balance through the restoration and regeneration of functional hair cells and non-sensory support cells within the inner ear.

Initial Public Offering

On February 17, 2021, the Company completed an initial public offering ("IPO"), issuing and selling 7,062,000 shares of common stock at a public offering price of $18.00 per share, and on February 24, 2021, the Company issued and sold an additional 600,000 shares pursuant to the underwriters' partial exercise of their option to purchase additional shares. The aggregate net proceeds received by the Company from the offering were $125.0 million. Upon closing of the IPO, all outstanding shares of convertible preferred stock automatically converted into shares of common stock. In advance of the IPO, on February 5, 2021, the Company's board of directors approved a 1-for-5.3 reverse stock split of the Company's common stock. All share and per share amounts in the consolidated financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to the reverse stock split.

Risks and Uncertainties

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including but not limited to, risks associated with completing preclinical studies and clinical trials, obtaining regulatory approvals for product candidates, development by competitors of new biopharmaceutical products, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Programs currently under development will require significant additional research and development efforts, including preclinical and clinical testing and will need to obtain regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. 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 is also subject to additional risks and uncertainties related to the ongoing COVID-19 pandemic and other macroeconomic and geopolitical events, which collectively have caused and may continue to cause major disruptions to businesses and economies worldwide.

The worldwide COVID-19 pandemic has affected and may affect in the future the Company's ability to initiate and complete preclinical studies, delay the initiation and completion of the Company's current and planned clinical trials, disrupt regulatory activities or have other adverse effects on the Company's business, results of operations, financial condition and prospects. In addition, the pandemic has caused substantial disruption to global supply chains and may adversely impact economies worldwide, both of which could adversely affect the Company's business, operations and ability to raise funds to support its operations. For example, due to increased quarantine mandates in China, the receipt of shipments and data from some of the Company's vendors and CROs were more difficult and unpredictable during the first half of 2022. This caused some delays in preclinical studies for the Company's gene therapy programs.

The Company cannot be certain what the overall impact of the COVID-19 pandemic will be on its business. The extent of the impact of COVID-19 on its business will depend on the length and severity of the pandemic, including the extent there is any resurgence of the COVID-19 virus or any variant strains of the virus, the availability and effectiveness of vaccines and the impact of the foregoing on its preclinical studies, current and planned clinical trials, employees and vendors, which is uncertain and cannot be predicted. The pandemic has the potential to adversely affect its business, financial condition, results of operations and prospects.

In addition, U.S. and global financial markets have experienced disruption due to various macroeconomic and geopolitical events. These include, but are not limited to, rising inflation, the risk of a recession and other ongoing global conflicts. The Company cannot predict at this time to what extent it and its collaborators, employees, suppliers, contract manufacturers and/or vendors could potentially be negatively impacted by these events.

Liquidity

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including but not limited to, risks associated with completing preclinical studies and clinical trials, obtaining regulatory approvals for product candidates, development by competitors of new biopharmaceutical products, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Programs currently under development will require significant additional research and development efforts, including preclinical and clinical testing and will need to obtain regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

In accordance with Accounting Standards Update ("ASU") No. 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern (Subtopic 205-40)* ("ASU 2014-15"), management must evaluate whether there are conditions or events, when 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. This evaluation initially does not take into consideration the potential mitigating effect of management's plans that have not been fully implemented as of the date the financial statements are issued. When substantial doubt exists under this methodology, management evaluates whether the mitigating effect of its plans sufficiently alleviates substantial doubt about the company's ability to continue as a going concern. The mitigating effect of management's plans, however, is only considered if both (1) it is probable that the plans will be effectively implemented within one year after the date that the financial statements are issued, and (2) it is probable that the plans, when implemented, will mitigate the relevant conditions or events that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued. Generally, to be considered probable of being effectively implemented, the plans must have been approved before the date that the financial statements are issued.

The Company's financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities in the ordinary course of business. Since inception, the Company has incurred recurring losses and negative cash flows from operations in each period and on an aggregate basis. As of December 31, 2022, the Company had an accumulated deficit of $277.5 million. The Company expects its operating losses and negative operating cash flows to continue for the foreseeable future as it continues to invest significantly in the research and development of its product candidates, preclinical and clinical development and its platform.

As of December 31, 2022, the Company had $104.6 million of cash, cash equivalents and available-for-sale securities which together with net proceeds raised under the Open Market Sale Agreement ("the Sales Agreement") subsequent to December 31, 2022, may not be sufficient to fund its operations for at least twelve months from the date of issuance of these consolidated financial statements which raises substantial doubt about the Company's ability to continue as a going concern. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. The Company has plans in place to mitigate this risk, which primarily consist of pursuing additional funding through the sale of equity, debt financings or other capital sources, including collaborations with other third parties, as well as by reducing cash expenditures. There is no guarantee that the Company will be successful in these mitigation efforts. The Company's inability to raise capital as and when needed could have a negative impact on its financial condition and ability to pursue its business strategies. There can be no assurance that the current operating plan will be achieved or that additional funding will be available on terms acceptable to the Company, or at all.

The accompanying consolidated financial statements have been prepared on a going concern basis, which contemplates the realization of assets and satisfaction of liabilities in the ordinary course of business. The consolidated financial statements do not include any adjustments relating to the recoverability and classification of recorded asset amounts or the amounts and classification of liabilities that might result from the outcome of this uncertainty.

2. Summary of Significant Accounting Policies

Basis of Presentation

These consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries, Decibel Securities Corporation and Decibel Therapeutics Australia Pty. All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Actual results could materially differ from those estimates. Management considers many factors in selecting appropriate financial accounting policies and controls, and in developing the estimates and assumptions that are used in the preparation of these consolidated financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes and management must select an amount that falls within that range of reasonable estimates. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the estimated cost to perform research which is an input into the measurement of research and development expenses recognized under the Company's collaboration agreement with Regeneron Pharmaceuticals, Inc. ("Regeneron"), the accrual of research and development expenses, stock-based compensation expenses, leases and income taxes. Estimates are periodically reviewed considering changes in circumstances, facts and historical experience. Actual results may differ from the Company's estimates.

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 in deciding how to allocate resources and assess performance. The Company and the Company's chief operating decision-maker, the Company's chief executive officer, view the Company's operations and manages its business as a single operating segment. All of the Company's long-lived assets are held in the United States.

Cash, Cash Equivalents and Restricted Cash

Cash equivalents are short-term, highly liquid investments that are readily convertible into cash, with original maturities of three months or less. Cash equivalents are mainly comprised of money market accounts invested in U.S. Treasury securities and agency bonds.

Restricted cash is comprised of deposits with a financial institution used to collateralize letters of credit related to the Company's lease arrangements. Restricted cash is presented as a component of prepaid expenses and other current assets and other assets on the consolidated balance sheets.

Cash, cash equivalents and restricted cash consisted of the following (in thousands):

	December 31,	
	2022	2021
Cash and cash equivalents	$ 34,607	$ 36,455
Restricted cash, current	38	—
Restricted cash, long-term	924	1,128
Total cash, cash equivalents and restricted cash as shown on the statement of cash flows	$ 35,569	$ 37,583

Available-For-Sale Securities

The Company classifies all of its investments as available-for-sale securities and reports them at fair value using quoted prices in active markets for similar securities. Unrealized gains and losses on available-for-sale securities are reported as accumulated other comprehensive loss, which is a separate component of stockholders' equity. The cost of securities sold is determined on a specific identification basis, and realized gains and losses are included in other income (expense), net within the consolidated statements of operations and comprehensive loss.

The Company regularly reviews all of its investments for other-than-temporary declines in estimated fair value. The Company's review includes the consideration of the cause of the impairment, including the creditworthiness of the security issuers, the number of securities in an unrealized loss position, the severity and duration of the unrealized losses, whether the

Company has the intent to sell the securities and whether it is more likely than not that the Company will be required to sell the securities before the recovery of their amortized cost basis. When the Company determines that the decline in estimated fair value of an investment is below the amortized cost basis and the decline is other-than-temporary, the Company reduces the carrying value of the security and records a loss for the amount of such decline. No such adjustments were necessary during the periods presented.

The Company classifies its available-for-sale securities as current assets on the consolidated balance sheets if they mature within one year from the balance sheet date, and long-term available-for-sale securities if they mature longer than one year from the balance sheet date.

Concentrations of Credit Risk and Significant Suppliers

Financial instruments that potentially expose the Company to credit risk primarily consist of cash, cash equivalents, restricted cash and available-for-sale securities. The Company maintains its cash, cash equivalents, restricted cash and available-for-sale securities balances with accredited financial institutions and, consequently, the Company does not believe it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company's cash management and investment policy limits investment instruments to U.S. Treasury and government securities with the objective to preserve capital and to maintain liquidity until the funds can be used in business operations. Bank accounts in the United States are insured by the Federal Deposit Insurance Corporation ("FDIC") up to $250,000. As of December 31, 2022 and 2021, the Company's primary operating accounts significantly exceeded the FDIC limits.

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients, other raw materials and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients, other raw materials and formulated drugs.

Off-Balance Sheet Arrangements

As of December 31, 2022, and 2021, the Company had no off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Fair Value Measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. The fair values of the Company's financial assets and liabilities reflect the Company's estimate of the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

To the extent the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reflected in the consolidated balance sheets for cash, accounts receivable, prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair values due to the short-term nature of

these assets and liabilities. Items measured at fair value on a recurring basis include cash equivalents and available-for-sales securities as of December 31, 2022 and 2021.

Accounts Receivable, net

The Company records accounts receivable for amounts invoiced to a collaborator, for which the Company has an unconditional right to consideration. For amounts to which the Company has an unconditional right to consideration but has not yet invoiced the collaborator, the Company records unbilled accounts receivable. The Company assesses the collectability for its accounts receivable and unbilled accounts receivable and records an allowance as deemed necessary. As of December 31, 2022 and 2021, no allowance was recorded. Accounts receivable and unbilled accounts receivable are presented in accounts receivable, net on the consolidated balance sheets.

Property and Equipment

Property and equipment is stated at cost, net of accumulated depreciation and amortization. Depreciation and amortization are calculated using the straight-line method over the estimated useful lives of the assets, which are as follows:

	Estimated Useful Life
Computer equipment and software	3 years
Furniture and fixtures	7 years
Laboratory equipment	5 years
Leasehold improvements	Shorter of useful life or remaining lease term

Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation and amortization are removed from the accounts and any resulting gain or loss is included in income (loss) from operations. Expenditures for repairs and maintenance that do not improve or extend the lives of the respective assets are charged to expense as incurred, while costs of major additions and betterments are capitalized.

Impairment of Long-Lived Assets

The Company periodically evaluates its long-lived assets, which consist of property and equipment, for impairment whenever events or changes in circumstances indicate that a potential impairment may have occurred. If such events or changes in circumstances arise, the Company compares the carrying amount of the long-lived assets to the estimated future undiscounted cash flows expected to be generated by the long-lived assets. If the estimated aggregate undiscounted cash flows are less than the carrying amount of the long-lived assets, an impairment charge, calculated as the amount by which the carrying amount of the assets exceeds the estimated fair value of the assets, is recorded. The estimated fair value of the long-lived assets is determined based on the estimated discounted cash flows expected to be generated from the long-lived assets.

Research and Development Costs and Accruals

Research and development costs are expensed as incurred. Research and development expenses are comprised of costs incurred in performing research and development activities, including salaries, stock-based compensation and benefits, laboratory supplies, depreciation on and maintenance of research equipment, manufacturing expenses and external costs of outside vendors engaged to conduct preclinical and clinical development activities and the allocable portions of facility costs, such as rent, utilities, repairs and maintenance, depreciation, and general support services. Additionally, the consideration the Company receives under its license and collaboration agreement with Regeneron is being recognized as a reduction to research and development expense (contra-research and development expense) in the Company's consolidated statements of operations and comprehensive loss based on the Company's progress towards completion of its research activities under the research plan (see Note 13).

Upfront payments and milestone payments made for the licensing of technology are expensed as research and development expenses in the period in which they are incurred. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

The Company records accruals for estimated ongoing research and development costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the preclinical studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining

the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Patent Costs

All patent-related costs incurred in connection with filing, maintaining and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses.

Stock-Based Compensation

The Company issues stock-based awards to employees, directors and non-employee consultants, generally in the form of stock options, restricted stock and restricted stock units ("RSUs"). The Company accounts for its stock-based compensation awards in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires stock-based payments to employees, qualifying directors and non-employees to be recognized as expense based on the fair value determined on the date of grant.

The Company issues equity awards with service-based and performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated requisite service period of the award, which is generally the vesting term. Compensation expense related to awards to employees, directors and non-employees with performance-based vesting conditions is recognized when it becomes probable that the performance conditions will be met using the accelerated attribution method. The Company has no awards with market-based conditions. The Company recognizes forfeitures as they occur.

The Company classifies stock-based compensation expense in the consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's salary and related costs are classified or in which the award recipient's service payments are classified, as applicable.

The Company determines the fair value of restricted stock and RSU awards in reference to the fair value of its common stock less any applicable purchase price. The Company estimates the fair value of its stock options using the Black-Scholes option pricing model, which requires inputs of subjective assumptions, including: (i) the expected volatility of its common stock, (ii) the expected term of the award, (iii) the risk-free interest rate, (iv) expected dividends and (v) the fair value of its common stock. Due to the lack of a public market for the trading of its common stock prior to the completion of its IPO and a lack of company-specific historical and implied volatility data, the Company bases the estimate of expected volatility on the historical volatilities of a representative group of publicly traded companies. For these analyses, the Company selects companies with comparable characteristics and with historical share price information that approximates the expected term of the stock-based awards. The Company computes the historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period that approximates the calculated expected term of its stock options. The Company will continue to apply this method until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The Company estimates the expected term of its stock options granted to employees and directors using the simplified method, whereby the expected term equals the average of the vesting term and the original contractual term of the option. The Company utilizes this method as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The expected dividend yield is assumed to be zero, as the Company has no current plans to pay any dividends on its common stock. The Company has elected to use the expected term for stock options granted to non-employees, using the simplified method, as the basis for the expected term assumption. However, the Company may elect to use either the contractual term or the expected term for stock options granted to non-employees on an award-by-award basis.

Subsequent to the completion of the IPO, the fair value of the common stock underlying the Company's stock-based awards is determined based on the trading price of its common stock on the Nasdaq Global Select Market on the date of grant.

Leases

The Company adopted FASB ASU No. 2016-02, Leases ("ASC 842"), effective January 1, 2022 using the required modified retrospective approach and utilizing the effective date as its date of initial application. Prior periods are presented in accordance with previous guidance in FASB ASC Topic 840, Leases.

The Company evaluates whether an arrangement is or contains a lease at contract inception. If a contract is or contains a lease, lease classification is determined at lease commencement, which represents the date at which the underlying asset is

made available for use by the Company. The Company's lease terms are generally measured as the respective lease's noncancelable term and exclude any optional extension terms as the Company is not reasonably certain to exercise such options. The Company elected the short-term lease exemption and therefore does not recognize lease liabilities and right-of-use assets for lease arrangements with original lease terms of twelve months or less.

Lease liabilities represent the Company's obligation to make lease payments under a lease arrangement. Lease liabilities are measured as the present value of fixed lease payments, discounted using an incremental borrowing rate, as interest rates implicit in the Company's lease arrangements are generally not readily determinable. The Company elected the practical expedient to not separate lease and non-lease components for its real estate leases and therefore both are considered when determining the lease payments in a lease arrangement. Variable lease costs are expensed as incurred.

The incremental borrowing rate represents the interest rate at which the Company could borrow a fully collateralized amount equal to the lease payments, over a similar term, in a similar economic environment. The Company determines the incremental borrowing rate at lease commencement, generally using a synthetic credit rating based on the Company's financial position and negative cash flows, factoring in adjustments for additional risks based on the Company's economic condition, a survey of comparable companies with similar credit and financial profiles, as well as additional market risks, as may be applicable.

Right-of-use assets represent the Company's right to use an underlying asset over its lease term. Right-of-use assets are initially measured as the associated lease liability, adjusted for prepaid rent and tenant incentives. The Company remeasures right-of-use assets and lease liabilities when a lease is modified, and the modification is not accounted for as a separate contract. A modification is accounted for as a separate contract if the modification grants the Company an additional right of use not included in the original lease agreement and the increase in lease payments is commensurate with the additional right of use. The Company assesses its right-of-use assets for impairment consistent with its policy for impairment of long-lived assets held and used in operations.

Income Taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the consolidated financial statements or tax returns. Deferred tax assets and liabilities are determined based on the difference between the consolidated financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies. Should the actual amounts differ from these estimates, the amount of the Company's valuation allowance could be materially impacted. Changes in these estimates may result in significant increases or decreases to the tax provision in a period in which such estimates are changed, which in turn would affect net income or loss.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. Derecognition of a tax position that was previously recognized occurs when the Company subsequently determines that a tax position no longer meets the more likely than not threshold. To the extent an income tax provision is necessary, the provision for income taxes would include the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties. The provision for income taxes includes the effects of any resulting tax reserves or unrecognized tax benefits that are considered appropriate as well as the related net interest and penalties.

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity that result from transactions and economic events other than those with stockholders. Other comprehensive loss for all periods presented consists solely of unrealized gains (losses) on available-for-sale securities.

Revenue Recognition

The Company recognizes revenue from contracts with customers under FASB ASC Topic 606, *Revenue from Contracts with Customers* ("ASC 606"). The Company has not had any transactions that fall within the scope of ASC 606, but does use ASC 606 by analogy for the measurement and recognition of contra-research and development expense under its collaboration agreement, which is accounted for under FASB ASC Topic 808, *Collaborative Agreements* ("Topic 808"). Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, the Company will perform the following five steps: (i) identification of the contract(s) with the customer, (ii) identification of the promised goods or services in the contract and determination of whether the promised goods or services are performance obligations, (iii) measurement of the transaction price, (iv) allocation of the transaction price to the performance obligations and (v) recognition of revenue when (or as) the Company satisfies each performance obligation.

The Company will account for a contract with a customer that is within the scope of ASC 606 when all of the following criteria are met: (i) the arrangement has been approved by the parties and the parties are committed to perform their respective obligations, (ii) each party's rights regarding the goods or services to be transferred can be identified, (iii) the payment terms for the goods or services to be transferred can be identified, (iv) the arrangement has commercial substance and (v) collection of substantially all of the consideration to which the Company will be entitled in exchange for the goods or services that will be transferred to the customer is probable.

The Company estimates the transaction price based on the amount of consideration the Company expects to be received for transferring the promised goods or services in the contract. The consideration may include both fixed consideration and variable consideration. For each arrangement that includes variable consideration, the Company evaluates the amount of the potential payments and the likelihood that the payments will be received. The Company utilizes either the most likely amount method or expected value method to estimate the transaction price based on which method better predicts the amount of consideration expected to be received. If it is probable that a significant revenue reversal would not occur, the variable consideration is included in the transaction price.

For arrangements that include development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. At the end of each reporting period, the Company re-evaluates the probability of achievement of such milestones and any related constraint, and if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect collaboration revenue and net loss in the period of adjustment.

For sales-based royalties, including milestone payments based on the level of sales, the Company determines whether the sole or predominant item to which the royalties relate is a license. When the license is the sole or predominant item to which the sales-based royalty relates, the Company recognizes revenue at the later of: (i) when the related sales occur or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

The Company allocates the transaction price to each performance obligation based on the relative estimated standalone selling price of the performance obligations. The Company must develop assumptions that require judgment to determine the standalone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the standalone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs. Certain variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated to each performance obligation are consistent with the amounts the Company would expect to receive for each performance obligation.

For performance obligations which consist of licenses and other promises, the Company utilizes judgment to assess the nature of the combined performance obligation in order to determine whether the combined performance obligation is satisfied over time or at a point in time. The Company determines the appropriate method of measuring progress of combined performance obligations satisfied over time for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company will recognize revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license.

Collaboration Agreements

The Company analyzes its collaboration arrangements to assess whether they are within the scope of Topic 808 to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards that are dependent on the commercial success of such activities. To the extent the arrangement is within the scope of Topic 808, the Company assesses whether aspects of the arrangement between the Company and its collaboration partner are within the scope of other accounting literature, including ASC 606.

If it is concluded that some or all aspects of the arrangement represent a transaction with a customer, the Company will account for those aspects of the arrangement within the scope of ASC 606. Pursuant to ASC 606, a customer is a party that has contracted with an entity to obtain goods or services that are an output of the entity's ordinary activities in exchange for consideration. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services.

ASC 808 provides guidance for the presentation and disclosure of transactions in collaborative arrangements, but it does not provide recognition or measurement guidance. Therefore, if the Company concludes a counterparty to a transaction is not a customer or otherwise not within the scope of ASC 606, the Company considers the guidance in other accounting literature, including the guidance in ASC 606, as applicable or by analogy to account for such transaction. The classification of transactions under the Company's arrangements is determined based on the nature and contractual terms of the arrangement along with the nature of the operations of the participants. To date, the Company has entered into a collaboration agreement with Regeneron (see Note 13).

CARES Act

The CARES Act provided refundable employee retention credits, which could be used to offset payroll tax liabilities. On March 11, 2021, President Biden signed the American Rescue Plan Act ("ARPA"). The ARPA includes several provisions, such as measures that extend and expand the employee retention credit, previously enacted under the CARES Act, through December 31, 2021.

Measures not related to income-based taxes within the CARES Act include (1) allowing an employer to pay its share of Social Security payroll taxes that would otherwise be due from the date of enactment through December 31, 2020 over the following two years and (2) allowing eligible employers subject to closure due to the COVID-19 pandemic to receive a 50% credit on qualified wages against their employment taxes each quarter, with any excess credits eligible for refunds.

The Company accounts for the grant under ASU No. 2021-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance* ("ASU 2021-10"). During the year ended December 31, 2021, the Company recorded an employee retention credit of $0.9 million upon completion of an analysis providing reasonable assurance that it met the conditions set forth in the CARES Act and it was reasonably assured that it will receive the employee retention credit. The employee retention credit was recorded in research and development expenses and general and administrative expenses in the manner in which the qualified wages and related costs were classified. No such additional amounts were recorded during the year ended December 31, 2022. The cash payments related to the credit were received in January 2023, and accordingly the credit was reflected in other current assets on the consolidated balance sheet for the year ended December 31, 2022.

Research and Development Tax Incentive

The Company is eligible under the AusIndustry Research and Tax Development Tax Incentive Program to obtain a cash amount from the Australian Taxation Office ("ATO"). The tax incentive is available to the Company on the basis of specific criteria with which the Company must comply related to research and development expenditures in Australia. The Company accounts for the grant under ASU No. 2021-10. The Company recognizes the Research and Development Tax Incentive (grant) as it incurs costs eligible for reimbursement under the AusIndustry Research and Tax Development Tax Incentive Program when it is reasonably assured that the grant funding will be received, as evidenced through enrollment in the program and when the applicable conditions under the program have been met. During the years ended December 31, 2022 and 2021, respectively, the Company recorded $0.2 million and $0.6 million, respectively, of research and development tax incentives as contra-research and development expense over the periods in which the Company recognized the eligible research and development activities taking place in Australia.

Net Income (Loss) per Share

The Company follows the two-class method when computing net income (loss) per share attributable to common stockholders as the Company has issued shares that meet the definition of participating securities. Net income (loss) allocable

to participating securities is calculated as net income (loss) less cumulative dividends on preferred stock accrued during the period, whether or not declared, and increases or decreases in the carrying value of preferred securities, including gains or losses on extinguishment. In determining net income (loss) attributable to common stockholders, the two-class method requires income (loss) allocable to participating securities for the period to be allocated between common and participating securities based upon their respective rights to share in the earnings as if all income (loss) allocable for the period had been distributed. The Company's convertible preferred stock participates in any dividends declared by the Company and are therefore considered to be participating securities. During periods of loss, there is no allocation required under the two-class method since the participating securities do not have a contractual obligation to fund the losses of the Company.

Basic net income (loss) per share attributable to common stockholders is computed by dividing the net income (loss) attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) per share attributable to common stockholders is computed by dividing the net income (loss) attributable to common stockholders by the weighted average number of shares of common stock outstanding for the period, including the effect of potentially dilutive common stock.

Emerging Growth Company Status

The Company is an emerging growth company ("EGC"), as defined in the Jumpstart Our Business Startups Act ("JOBS Act") and may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not EGCs. The Company may take advantage of these exemptions until it is no longer an EGC under Section 107 of the JOBS Act, which provides that an EGC can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. The Company has elected to use the extended transition period for complying with new or revised accounting standards, and as a result of this election, the consolidated financial statements may not be comparable to companies that comply with public company FASB standards' effective dates. The Company may take advantage of these exemptions up until December 31, 2026 or such earlier time that it is no longer an EGC.

Recently Adopted Accounting Pronouncements

In February 2016, the FASB issued ASC 842, which replaces the existing guidance for leases. ASC 842 requires the identification of arrangements that should be accounted for as leases by lessees. In general, for lease arrangements exceeding a twelve-month term, these arrangements must now be recognized as assets and liabilities on the balance sheet of the lessee. Under ASC 842, a right-of-use asset and lease obligation will be recorded for all leases, whether operating or financing, while the income statement will reflect lease expense for operating leases and amortization/interest expense for financing leases. The balance sheet amount recorded for existing leases at the date of adoption of ASC 842 must be calculated using the applicable incremental borrowing rate at the date of adoption. The Company adopted ASC 842 using the modified retrospective approach effective January 1, 2022. The Company elected the package of practical expedients which allows entities to not reassess (i) whether an arrangement is or contains a lease, (ii) the classification of its leases, and (iii) the accounting for initial direct costs. Further, the Company elected, by class of underlying asset, the short-term lease exception for leases with terms of twelve months or less. In doing so, the Company did not recognize a lease liability or right-of-use asset on its balance sheets for such short-term leases. Finally, the Company elected, by class of underlying asset, the practical expedient to not separate lease and non-lease components. The impact of adoption is summarized in the table below (in thousands):

	As Reported December 31, 2021	Impact of Adoption	As Adopted January 1, 2022
Operating lease right-of-use assets	—	11,485	11,485
Finance lease right-of-use assets	—	235	235
Property and equipment, net	5,611	(235)	5,376
Accrued expenses and other current liabilities	7,712	(213)	7,499
Deferred rent and lease incentive obligation, current	696	(696)	—
Operating lease liabilities, current	—	3,484	3,484
Finance lease liabilities, current	—	213	213
Deferred rent and lease incentive obligation, long-term	4,208	(4,208)	—
Operating lease liabilities, long-term	—	12,905	12,905
Finance lease liabilities, long-term	—	19	19
Other long-term liabilities	1,611	(19)	1,592

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* ("ASU 2019-12"), which is intended to simplify the accounting for income taxes. ASU 2019-12 removes certain exceptions related to the approach for intra-period tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also clarifies and simplifies other aspects of accounting for income taxes. The Company adopted ASU 2019-12 on January 1, 2022. The adoption did not have a material effect on the Company's consolidated financial statements and related disclosures.

In May 2021, the FASB issued ASU No. 2021-04, *Earnings Per Share (Topic 260), Debt — Modifications and Extinguishments (Subtopic 470-50), Compensation — Stock Compensation (Topic 718), and Derivatives and Hedging — Contracts in Entity's Own Equity (Subtopic 815-40)* ("ASU 2021-04"). ASU 2021-04 clarifies and reduces diversity in an issuer's accounting for modifications or exchanges of freestanding equity-classified written call options, including warrants, that remain equity-classified after modification or exchange. ASU 2021-04 requires an entity to treat a modification or an exchange of a freestanding equity-classified written call option that remains equity-classified after the modification or exchange as an exchange of the original instrument for a new instrument and provides guidance on measuring and recognizing the effect of a modification or an exchange. The Company adopted ASU 2021-04 on January 1, 2022. The adoption did not have a material impact on the Company's consolidated financial statements and related disclosures.

In November 2021, the FASB issued ASU No. 2021-10. ASU 2021-10 increases the transparency of transactions with the government that are accounted for by applying a grant or contribution accounting model, and it aims to reduce diversity that currently exists in the recognition, measurement, presentation, and disclosure of government assistance received by business entities due to the lack of specific authoritative guidance in GAAP. ASU 2021-10 requires an entity to provide information regarding the nature of the transaction with a government and the related accounting policy used to account for this transaction, the line item on the consolidated balance sheet and consolidated statement of operations and comprehensive loss that are affected by the transaction and the amounts applicable to each financial statement line item, and the significant terms and conditions of the transaction, including commitments and contingencies. The Company adopted ASU 2021-10 on January 1, 2022 using the prospective approach. The adoption did not have a material effect on the Company's consolidated financial statements and related disclosures.

Recently Issued Accounting Pronouncements

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326)—Measurement of Credit Losses on Financial Instruments,* which has been subsequently amended by ASU No. 2018-19, ASU No. 2019-04, ASU No. 2019-05, ASU No. 2019-10, ASU No. 2019-11 and ASU No. 2020-03 ("ASU 2016-13"). The provisions of ASU 2016-13 modify the impairment model to utilize an expected loss methodology in place of the currently used incurred loss methodology and require a consideration of a broader range of reasonable and supportable information to inform credit loss estimates. ASU 2016-13 is effective for the Company on January 1, 2023. The Company does not expect the adoption to have a material effect on the Company's consolidated financial statements and related disclosures.

In August 2020, the FASB issued ASU No. 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging Contracts in Entity's Own Equity (Subtopic 815-40)* ("ASU 2020-06"), which reduces the number of accounting models for convertible debt instruments and convertible preferred stock as well as amends the derivatives scope exception for contracts in an entity's own equity. ASU 2020-06 is effective for the Company on January 1, 2024, with early adoption permitted. The Company is currently evaluating the potential impact that this standard may have on its consolidated financial statements and related disclosures.

3. Fair Value Measurements

The Company measures the following financial assets at fair value on a recurring basis. The fair value of these assets was determined as follows (in thousands):

	Balance at December 31, 2022	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money market mutual funds	$ 34,059	$ 34,059	$ —	$ —
Total cash equivalents	$ 34,059	$ 34,059	$ —	$ —
Available-for-sale securities:				
U.S. Treasury securities	$ 36,246	$ —	$ 36,246	$ —
U.S. Agency bonds	22,523	—	22,523	—
U.S. Agency discount notes	11,185	—	11,185	—
Total available-for-sale securities	$ 69,954	$ —	$ 69,954	$ —

	Balance at December 31, 2021	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money market mutual funds	$ 31,726	$ 31,726	$ —	$ —
Total cash equivalents	$ 31,726	$ 31,726	$ —	$ —
Available-for-sale securities:				
U.S. Treasury securities	$ 61,373	$ —	$ 61,373	$ —
Corporate debt securities	33,806	—	33,806	—
U.S. Agency bonds	15,114	—	15,114	—
Commercial paper	1,999	—	1,999	—
Total available-for-sale securities	$ 112,292	$ —	$ 112,292	$ —
Available-for-sale securities, long-term:				
U.S. Treasury securities	$ 13,547	$ —	$ 13,547	$ —
Total available-for-sale securities, long-term	$ 13,547	$ —	$ 13,547	$ —

Money market funds were valued by the Company using quoted prices in active markets for identical securities, which represent a Level 1 measurement within the fair value hierarchy. The Company's available-for-sale securities were valued based on Level 2 inputs and in determining the fair value the Company relied on quoted prices for similar securities in active markets or other inputs that are observable or can be corroborated by observable market data. During the years ended December 31, 2022 and 2021, there were no changes in valuation techniques or transfers between Level 1, Level 2 and Level 3.

There were no liabilities measured at fair value on a recurring basis as of December 31, 2022 or 2021.

4. Available-For-Sale Securities

The following table summarizes the Company's available-for-sale securities (in thousands):

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Available-for-sale securities:				
U.S. Treasury securities	$ 36,452	$ —	$ (206)	$ 36,246
U.S. Agency bonds	22,550	8	(35)	22,523
U.S. Agency discount notes	11,175	10	—	11,185
Total available-for-sale securities	$ 70,177	$ 18	$ (241)	$ 69,954

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Available-for-sale securities:				
U.S. Treasury securities	$ 61,450	$ —	$ (77)	$ 61,373
Corporate debt securities	33,814	—	(8)	33,806
U.S. Agency bonds	15,123	—	(9)	15,114
Commercial paper	1,999	—	—	1,999
Total available-for-sale securities	$ 112,386	$ —	$ (94)	$ 112,292
Available-for-sale securities, long-term:				
U.S. Treasury securities	$ 13,585	$ —	$ (38)	$ 13,547
Total available-for-sale securities, long-term	$ 13,585	$ —	$ (38)	$ 13,547

The Company had 25 investments in available-for-sale securities in an unrealized loss position as of December 31, 2022 with a fair value of $48.1 million. The Company had 43 investments in available-for-sale securities in an unrealized loss position as of December 31, 2021 with a fair value of $120.3 million. These investments were in a loss position for less than 12 months and the Company considered the loss to be temporary in nature. The Company considered the decline in market value for these securities to be primarily attributable to economic and market conditions. As of December 31, 2022 and 2021, the Company did not intend to sell, and it was not more likely than not that the Company would be required to sell the investments that were in an unrealized loss position before recovery of their amortized cost basis. Accordingly, the Company did not recognize any other-than-temporary impairments related to its available-for-sale securities in an unrealized loss position. As of December 31, 2022, the Company did not hold any investments that matured beyond one year, and as of December 31, 2021, the Company did not hold any investments that matured beyond five years. During the years ended December 31, 2022 and 2021, the Company did not sell any available-for-sale securities and therefore did not recognize any realized gains or losses.

5. Property and Equipment, Net

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

	December 31,	
	2022	2021
Leasehold improvements	$ 7,096	$ 7,096
Laboratory equipment	3,406	3,339
Computer equipment and software	212	212
Furniture and fixtures	947	947
Construction in progress	40	—
Total property and equipment	11,701	11,594
Accumulated depreciation	(7,175)	(5,983)
Property and equipment, net	$ 4,526	$ 5,611

The Company incurred depreciation expense of $1.5 million and $1.4 million for the years ended December 31, 2022 and 2021, respectively.

6. Accrued Expenses and Other Current Liabilities

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

	Years Ended December 31,	
	2022	2021
Accrued research and development expenses	$ 3,469	$ 3,152
Accrued compensation and related expenses	2,883	2,932
Accrued professional fees	1,170	380
Other accrued expenses	887	1,035
Equipment financing, current	—	213
	$ 8,409	$ 7,712

7. Leases

Operating Leases

In July 2016, the Company entered into an operating lease for its facility in Boston, Massachusetts. Under the terms of the lease agreement, rent payments commenced in June 2017 with base rent in the first lease year of $2.1 million, subject to annual increases of 3.0% over the lease term through June 2027. The Company is also obligated to pay its ratable portion of operating expenses and taxes. The Company has the right to extend the lease for one additional five-year period at a market rental rate as determined by the landlord and agreed to by the Company. The lease is secured by a letter of credit in the amount of $0.5 million. In conjunction with the lease, the landlord provided the Company with a $5.3 million tenant improvement allowance.

In September 2019, the Company entered into an operating lease under which the Company leased additional office space from a separate third-party tenant under a sublease agreement at its existing facility. Under the terms of the lease agreement, rent payments commenced in December 2019 with base rent in the first lease year of $1.2 million, subject to annual rent escalation over the lease term through January 2027. The sublease is secured by a letter of credit in the amount of $0.3 million.

In January 2020, the Company entered into a sublease agreement to sublease a portion of its existing office and laboratory space to a third-party. The lease term commenced in March 2020 with an original term of 24 months. Annual base rent was $1.1 million for each year during the sublease term. The sublessee was obligated to pay its ratable portion of operating expenses during the sublease term. Subject to the Company's consent, the sublease provided the sublessee one option to extend for up to one year, subject to a 3.0% rent increase. In May 2021, the sublessee exercised its right to extend the sublease term through October 31, 2022. Pursuant to the extension, base rent was $1.7 million for each year during the extension term. The sublessee provided a security deposit of $0.2 million in cash which was presented as a component of accrued expenses and other current liabilities on the consolidated balance sheet. Payments received under the sublease were recorded as a reduction to rent expense in the consolidated statements of operations and comprehensive loss.

In January 2022, the Company entered into a sublease agreement to sublease an additional portion of its existing office space to a third-party. The lease term commenced in February 2022 with an original term of six months. Base rent over the term amounted to $0.5 million. The sublease granted the sublessee the right to extend for two terms of three months each at the same base rent per month for an additional $0.3 million for each term. In June 2022, the sublessee exercised its first right to extend the sublease term and in September 2022, the sublessee exercised its second right to extend the sublease term. In January 2023, the Company and sublessee amended the sublease agreement to extend the sublease term through May 2023 at the same base rent per month. There is no rent escalation under the amended sublease and there is no option to further extend the term of the sublease agreement. The sublessee prepaid the last month's rent of $0.1 million, which is presented as a component of accrued expenses and other current liabilities on the consolidated balance sheet. Payments received under the sublease are recorded as a reduction to rent expense in the consolidated statements of operations and comprehensive loss.

Finance Leases

In July 2020, the Company entered into a financing transaction with a third-party leasing company. Pursuant to the transaction, the Company transferred title and interest in certain laboratory equipment to the third party in exchange for a one-time cash payment of $0.5 million and agreed to lease the laboratory equipment back from the third party for $0.2 million per year for 2.5 years. The Company concluded the lease was a capital lease under ASC 840 and a finance lease after the Company's adoption of ASC 842.

The components of lease cost for the year ended December 31, 2022 were as follows (in thousands):

Operating lease cost	$	2,917
Variable lease cost		782
Short-term lease cost		17
Finance lease cost:		
Amortization of right-of-use assets		201
Interest expense on lease liabilities		14
Sublease income		(2,476)
Total lease cost	$	1,455

Supplemental cash flow information related to the Company's leases for the year ended December 31, 2022 were as follow (in thousands):

Cash paid for amounts included in the measurement of lease liabilities		
Operating cash flows for operating leases	$	3,616
Operating cash flows for finance leases	$	14
Financing cash flows for finance leases	$	213

Future minimum lease payments under the Company's noncancelable leases as of December 31, 2022 were as follows (in thousands):

	Operating Leases	Finance Leases
2023	$ 3,705	$ 19
2024	3,796	—
2025	3,889	—
2026	3,984	—
2027	1,350	—
Total lease payments	16,724	19
Present value adjustment	(2,690)	—
Present value of lease payments	$ 14,034	$ 19

As of December 31, 2022, the Company's operating leases had a weighted-average remaining lease term of 4.3 years and weighted average incremental borrowing rate of 8.7%. As of December 31, 2022, the Company's finance lease had a weighted average remaining lease term of 0.1 years and weighted average incremental borrowing rate of 10.0%.

8. Commitments and Contingencies

License Agreement with University of Florida Research Foundation

In October 2020, the Company entered into a license agreement with University of Florida Research Foundation, Incorporated ("UFRF"), which was amended in June 2022, relating to certain patent rights related to compositions and methods for expressing otoferlin (the "UFRF License"). Under the UFRF License, the Company acquired an exclusive, sublicensable, worldwide license to make, have made, use, sell, have sold, and import products covered by the licensed patent rights. Under the UFRF License, UFRF retains the right for itself and any non-profit institution or governmental entity to practice and have practiced certain of the licensed intellectual property rights for research, clinical, and educational purposes. The UFRF License is also subject to pre-existing rights of the U.S. government.

The Company paid UFRF an upfront fee of $0.1 million and agreed to pay UFRF an additional $0.1 million following the issuance of the first patent under the UFRF License. In addition, under the terms of the UFRF License, the Company is required to pay to UFRF certain nominal annual license maintenance fees until the first year in which it sells a licensed product. Under the UFRF License, the Company has agreed to pay UFRF a low single-digit royalty on annual net sales of licensed products. The obligation to pay royalties continues on a licensed-product-by-licensed-product and country-by-country basis until the expiration of the last of the patent rights licensed under the UFRF License. In addition, the Company is obligated to make contingent milestone payments to UFRF totaling up to $0.8 million in the aggregate upon the achievement of certain clinical and regulatory milestones and up to an additional $11.2 million in the aggregate upon the achievement of certain commercial sales milestones, in each case, whether achieved by the Company or its sublicensee. No clinical, regulatory or commercial milestones have been achieved to date. In the event that the Company sublicenses the licensed patent rights, UFRF is also entitled to receive a percentage of the sublicensing revenue received by the Company. Under the UFRF License, the Company is obligated to use commercially reasonable efforts to develop, commercialize and

maintain supply of licensed product. The Company also agreed to meet specified development, regulatory and commercialization milestones for the licensed patent rights by specified dates, subject to extensions that may be granted by UFRF under certain circumstances. UFRF has the right to terminate the license if the Company fails to perform its diligence obligations.

The agreement will continue on a licensed-product-by-licensed-product and country-by-country basis until the last to expire of the patent rights under the UFRF License. The Company may terminate the agreement by providing prior written notice to UFRF. UFRF has the right to terminate the agreement if the Company fails to make any payments, bring action or proceeding against UFRF or otherwise breach the agreement and fail to cure such breach within a specified grace period. In addition, the agreement will immediately terminate upon certain events of insolvency of either party.

All payments made to UFRF have been expensed as research and development expenses in the consolidated statements of operations and comprehensive loss. The consolidated financial statements as of December 31, 2022 and 2021 do not include liabilities with respect to this license agreement as the Company has not yet generated revenue and the achievement of certain milestones is not probable.

License Agreement with The Regents of The University of California

In October 2019, the Company entered into a license agreement with The Regents of the University of California ("UCSF") relating to certain patent rights related to compositions and methods for expressing otoferlin, which is referred to collectively as the UCSF License. Under the UCSF License, the Company acquired an exclusive, sublicensable, worldwide license to make, have made, use, sell, offer for sale and import products, services, and methods covered by the licensed patent rights, and to perform licensed processes. Under the UCSF License, UCSF retains the right to make, use and practice certain of the licensed intellectual property rights for research and educational purposes, and the right to license to other academic and nonprofit organizations to practice the patent rights for research and educational purposes. The UCSF License is also subject to pre-existing rights of the U.S. government and the National Institutes of Health.

The Company paid to UCSF a nominal upfront fee and agreed to pay UCSF an additional nominal fee following the issuance of the first patent under the UCSF License. In addition, under the terms of the UCSF License, the Company is required to pay to UCSF certain nominal annual license maintenance fees unless the Company is selling or otherwise exploiting licensed products or services paying royalties to UCSF on net sales for such licensed products or services. With respect to such royalty obligations, the Company agreed to pay UCSF low single-digit royalties on annual net sales of licensed products and services. The Company's obligation to pay royalties continues until the expiration or abandonment of the last of the patent rights licensed under the UCSF License. In addition, the Company is obligated to make contingent milestone payments to UCSF totaling up to $0.5 million upon the achievement of certain regulatory milestones and up to $5.0 million upon the achievement of certain commercial sales milestones whether achieved by the Company or its sublicensee. No regulatory or commercial milestones have been achieved to date. In the event that the Company sublicenses the licensed patent rights, UCSF is also entitled to receive a percentage of the sublicensing income received by the Company.

Under the UCSF License, the Company is obligated to diligently proceed with the development, manufacture and sale of at least one licensed product and/or service, and to earnestly and diligently market such licensed product and/or service after receipt of any requisite regulatory approvals and in quantities sufficient to meet market demand. The Company has also agreed to meet specified development, regulatory and commercialization milestones for the licensed patent rights by specified dates, subject to extensions that may be granted by UCSF under certain circumstances. UCSF has the right to revoke the Company's right to sublicense the UCSF License or reduce the license to a nonexclusive license if the Company is unable to perform its diligence obligations.

The agreement will continue until the last to expire or abandonment of the patent rights under the UCSF License. The Company may terminate the agreement by providing prior written notice to UCSF or it may terminate the rights under patent rights on a country-by-country basis by giving notice in writing to UCSF. UCSF has the right to terminate the agreement if the Company fails to make any payments, challenge any UCSF patent rights or otherwise materially breach the agreement and fail to cure such breach within a specified grace period.

All payments made to UCSF have been expensed as research and development expenses in the consolidated statements of operations and comprehensive loss. The consolidated financial statements as of December 31, 2022 and 2021 do not include liabilities with respect to this license agreement as the Company has not yet generated revenue and the achievement of certain milestones is not probable.

License Agreement with The Curators of the University of Missouri

In August 2019, the Company entered into a license agreement with The Curators of the University of Missouri (the "University of Missouri"), which was amended in February 2021 and May 2022, relating to certain patent rights related to the AAV vectors it is using in the gene therapies the Company is developing for congenital, monogenic hearing loss due to an otoferlin deficiency and due to a deficiency in another specified gene, which is referred to collectively as the University of Missouri License.

Under the University of Missouri License, the Company acquired an exclusive license to make, have made, use, sell, have sold, import, distribute or otherwise transfer products (the "licensed products"), covered by the licensed patent rights. The Company may sublicense the licensed patent rights with the University of Missouri's prior written approval. Under the University of Missouri License, the University of Missouri retains the right to make, use and practice certain of the licensed intellectual property rights for non-commercial research purposes and the right to license to nonprofit, academic or government institutions the patent rights for non-commercial research purposes. The University of Missouri License is also subject to pre-existing rights of the U.S. government and the National Institutes of Health.

The Company paid to the University of Missouri a $0.1 million upfront fee and agreed to pay the University of Missouri a nominal annual license maintenance fee. In addition, the Company agreed to pay to the University of Missouri a low single-digit royalty on annual net sales of licensed products sold regardless of where such licensed products are manufactured and an additional low single-digit royalty on annual net sales of licensed products that are sold outside of the United States but manufactured within the United States, with a specified minimum annual royalty requirement. The Company's obligation to pay royalties continues until the expiration or abandonment of the last of the patent rights licensed under the University of Missouri License. In addition, the Company is obligated to make milestone payments on a licensed-product-by-licensed-product basis to the University of Missouri totaling up to $0.8 million in the aggregate upon the achievement of certain development and regulatory milestones and up to $13.1 million in the aggregate upon the achievement of certain commercial sales milestones, whether achieved by the Company or its sublicensee. During the year ended December 31, 2022 the Company achieved and paid less than $0.1 million with respect to a regulatory milestone related to the Company's submission of an investigational new drug application ("IND"), for the Company's lead developmental gene therapy, DB-OTO. In the event that the Company sublicenses the licensed patent rights, the University of Missouri is also entitled to receive a tiered percentage of the sublicensing revenue received by the Company, which varies depending on the stage of development at which the Company enters into such sublicense.

Under the University of Missouri License, the Company is obligated to use reasonable commercial efforts to advance the licensed product towards commercialization. The Company has also agreed to meet specified development, regulatory and commercialization milestones for the licensed patent rights by specified dates. The University of Missouri has the right to unilaterally terminate the University of Missouri License or reduce the license to a nonexclusive license if the Company fails to meet such specified milestones.

The agreement will continue until the last to expire or abandonment of the patent rights under the University of Missouri License. The Company may terminate the agreement by providing prior written notice to the University of Missouri or upon the uncured material breach of the agreement by the University of Missouri. The University of Missouri has the right to terminate the agreement if the Company fails to make any payments, upon the occurrence of certain events of insolvency for the Company, challenge any University of Missouri patent rights or otherwise materially breach the agreement and fail to cure such breach within a specified grace period.

All payments made to the University of Missouri have been expensed as research and development expenses in the consolidated statements of operations and comprehensive loss. The consolidated financial statements as of December 31, 2022 and 2021 do not include liabilities with respect to this license agreement as the Company has not yet generated revenue and the achievement of certain milestones is not probable.

Purchase Orders

The Company has agreements with third parties for various services, including services related to preclinical operations and support, for which the Company is not contractually able to terminate for convenience to avoid future obligations to the vendors. Certain agreements provide for termination rights subject to termination fees or wind down costs. Under such agreements, the Company is contractually obligated to make certain payments to vendors, primarily to reimburse them for their unrecoverable outlays incurred prior to cancelation. The actual amounts the Company could pay in the future to the vendors under such agreements may differ from the purchase order amounts due to cancellation provisions.

Indemnification Agreements

The Company enters into standard indemnification agreements and/or indemnification sections in other agreements in the ordinary course of business. Pursuant to the agreements, the Company indemnifies, holds harmless, and agrees to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company's business partners. The term of these indemnification agreements is generally perpetual any time after execution of the agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements and/or sections is unlimited. The Company has never incurred costs to defend lawsuits or settle claims related to these indemnification agreements and/or sections. The Company does not believe that the outcome of any claims under indemnification arrangements will have a material effect on its financial position, results of operations or cash flows, and it had not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2022 or 2021.

Legal Proceedings

From time to time, the Company may become party to litigation or other legal proceedings as part of its ordinary course of business. As of December 31, 2022, the Company is not currently party to any material legal proceedings. At each reporting date, the Company evaluates whether or not a potential loss amount or a potential range of loss is probable and reasonably estimable under the provisions of FASB ASC Topic 450, *Contingencies*. The Company expenses as incurred the costs related to its legal proceedings.

9. Stockholders' Equity

As of December 31, 2022 and 2021, the Company's Certificate of Incorporation authorized the Company to issue 200,000,000 shares of common stock, $0.001 par value, and 5,000,000 shares of undesignated preferred stock, $0.001 par value per share.

The rights, preferences and privileges of the Company's common stock are as follows:

Voting

The holders of shares of common stock are entitled to one vote for each share of common stock held on all matters submitted to a vote of the Company's stockholders.

Dividends

The holders of shares of common stock are not entitled to receive dividends, unless declared by the Company's board of directors, subject to any preferential dividend or other rights of any then-outstanding preferred stock. No dividends have been declared or paid by the Company since its inception.

Liquidation

After the payment of all preferential amounts required to be paid to the holders of shares of the Company's then-outstanding preferred stock, the remaining assets of the Company available for distribution to its stockholders would be distributed among the holders of the shares of common stock, pro rata, based on the number of shares held by each such holder.

Common Stock Reserved

The Company had the following shares of common stock reserved for future issuance:

	December 31,	
	2022	2021
Shares reserved for exercise of outstanding stock options under the 2015 Stock Incentive Plan	2,155,577	2,540,963
Shares reserved for exercise of outstanding stock options under the 2021 Stock Incentive Plan	1,320,800	496,500
Shares reserved for vesting of restricted stock units granted under the 2021 Stock Incentive Plan	219,742	—
Shares reserved for future awards under the 2021 Stock Incentive Plan	1,561,034	1,221,593
Shares reserved for issuance under the 2021 Employee Stock Purchase Plan	815,556	566,037
Total shares of common stock reserved	6,072,709	4,825,093

At-the-market equity offering program

In March 2022, the Company filed a universal shelf registration statement on Form S-3 to register for sale from time to time up to $200.0 million of common stock, preferred stock, debt securities, warrants and/or units in one or more offerings. Further, in March 2022, the Company entered into an Open Market Sale Agreement℠ (the "Sales Agreement") with Jefferies LLC ("Jefferies") pursuant to which, from time to time, the Company may offer and sell shares of its common stock. Sales of common stock through Jefferies may be made by any method that is deemed an "at-the-market" offering as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. Jefferies is entitled to compensation at a rate equal to 3.0% of the gross proceeds from any shares of common stock sold under the Sales Agreement. In August 2022, the Company filed a prospectus supplement under its universal shelf registration for the offer and sale of shares of its common stock having an aggregate offering price up to $50.0 million pursuant to the Sales Agreement. As of December 31, 2022, the Company had not sold any shares of common stock pursuant to the Sales Agreement. Subsequent to December 31, 2022, the Company issued and sold a total of 50,482 shares under the Sales Agreement for aggregate net proceeds of $0.2 million after deducting commissions payable by the Company.

10. Convertible Preferred Stock

Immediately prior to the closing of its IPO, the Company had an aggregate of 155,398,078 shares of convertible preferred stock issued and outstanding which automatically converted into 16,662,011 shares of common stock upon the closing of its IPO. During the year ended December 31, 2021, in the period prior to the Company's IPO, $2.3 million of cumulative dividends were accrued and unpaid on the Company's convertible preferred stock. In connection with the completion of the Company's IPO and the conversion of the outstanding convertible preferred stock into common stock, the $2.3 million of accrued and unpaid dividends were eliminated. Subsequent to the closing of the Company's IPO, no shares of convertible preferred stock were issued or outstanding, and no dividends were accrued.

11. Stock-Based Compensation

2021 Stock Incentive Plan

In connection with its IPO, the Company adopted the 2021 Stock Incentive Plan (the "2021 Plan"), which became effective on February 11, 2021. The 2021 Plan allows the Company to grant stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards to Company's officers, employees, directors and other key persons (including consultants). The number of shares reserved for issuance under the 2021 Plan will be cumulatively increased each January 1 by 4% of the number of shares of the Company's common stock outstanding on the immediately preceding December 31 or such lesser number of shares determined by the Company's compensation committee. As of December 31, 2021, there were 1,718,093 shares of common stock authorized for issuance under the 2021 Plan and on January 1, 2022, the number of shares of common stock authorized for issuance under the 2021 Plan automatically increased by 998,079 shares. As of December 31, 2022, 1,540,542 shares were reserved for outstanding awards granted under the 2021 Plan and 1,561,034 shares remained available for issuance.

Terms of equity grants, including vesting requirements, are determined by the Board or the Compensation Committee of the Board, subject to the provisions of the applicable plan.

Shares of common stock may be withheld to satisfy applicable federal, state or local employment tax withholding obligations related to equity awards. Shares of common stock that are tendered to the Company by a participant to exercise an award are added to the number of shares of common stock available for future awards. Upon stock option exercise, the Company issues new shares and delivers them to the participant.

2015 Stock Incentive Plan

Prior to the effective date of the 2021 Plan, the Company granted equity awards to eligible employees, officers, directors, consultants and advisors under the 2015 Stock Incentive Plan (the "2015 Plan"). Subsequent to the effective date of the 2021 Plan, no further awards can be made under the 2015 Plan; however, awards outstanding under the 2015 Plan continue to be governed by the 2015 Plan. As of December 31, 2022, there were 2,155,577 shares reserved for outstanding awards granted under the 2015 Plan and no shares remained available for issuance.

As of the effective date of the 2021 Plan, the Company will not grant any further awards under the 2015 Plan. Shares that expire, are terminated, repurchased, surrendered or canceled under the 2015 Plan and the 2021 Plan without having been fully exercised are available for future awards under the 2021 Plan.

2021 Employee Stock Purchase Plan

In connection with its IPO, the Company adopted the 2021 Employee Stock Purchase Plan (the "2021 ESPP"), which was amended and restated in October 2022. Under the 2021 ESPP, eligible employees are able to purchase shares of common stock at a specified discount. As of December 31, 2021, there were 566,037 shares of common stock authorized for issuance under the 2021 ESPP. On January 1, 2022, the number of shares of common stock authorized for issuance under the 2021 ESPP automatically increased by 249,519 shares. As of December 31, 2022, no shares have been issued under the 2021 ESPP and as such, 815,556 shares remained available for issuance under the 2021 ESPP.

Restricted Stock Awards

A summary of the Company's restricted stock activity and related information is as follows:

	Number of Shares of Restricted Stock Awards	Weighted Average Grant Date Fair Value
Unvested as of December 31, 2021	12,537	$ 24.79
Vested	(12,519)	24.80
Canceled/Forfeited	(18)	15.37
Unvested as of December 31, 2022	—	$ —

No restricted stock awards were issued during the years ended December 31, 2022 or 2021.

The aggregate fair value of restricted stock awards that vested during the years ended December 31, 2022 and 2021 was $0.3 million and $0.6 million, respectively.

As of December 31, 2022, there was no unrecognized compensation cost related to any unvested restricted stock awards.

Restricted Stock Units

A summary of the Company's restricted stock unit activity and related information is as follows:

	Number of Restricted Stock Units	Weighted Average Grant Date Fair Value
Unvested as of December 31, 2021	—	$ —
Granted	313,185	3.50
Vested	—	—
Canceled/Forfeited	(93,443)	3.50
Unvested as of December 31, 2022	219,742	$ 3.50

The Company has granted RSUs to certain of its employees under the 2021 Plan, as part of its equity compensation program. Pursuant to the terms of the applicable award agreements, each RSU represents the right to receive one share of the Company's common stock. All restricted stock units outstanding as of December 31, 2022 will vest, if at all, upon the achievement of specified development milestones associated with the Company's DB-OTO program, provided the applicable employee remains continuously employed with the Company on the vesting date. Upon vesting, shares of the Company's common stock will be delivered to the employee, subject to the payment of applicable withholding taxes.

As of December 31, 2022, total unrecognized compensation cost related to the unvested restricted stock units was approximately $0.8 million, which will not be recognized until it becomes probable that the performance conditions will be met.

Stock Options

A summary of the Company's stock option activity and related information is as follows:

	Number of Stock Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
			(In years)	(In thousands)
Outstanding as of December 31, 2021	3,037,463	$ 5.34	8.9	$ 629
Granted	1,075,200			
Exercised	—			
Cancelled/forfeited	(636,286)			
Outstanding as of December 31, 2022	3,476,377	$ 4.76	7.4	$ 255
Exercisable as of December 31, 2022	1,671,073	$ 5.13	6.6	$ —
Vested and expected to vest as of December 31, 2022	3,476,377	$ 4.76	7.4	$ 255

The Company estimated the fair value of stock options at the date of grant using the Black-Scholes valuation model with the following assumptions:

	Year Ended December 31,	
	2022	2021
Risk-free interest rate	1.63 - 4.26%	0.82 - 1.34%
Expected annual dividend yield	0.00%	0.00%
Expected stock price volatility	86.7 - 94.1%	85.4 - 89.3%
Expected term (in years)	5.5 - 6.1	5.0 - 6.1

The weighted-average grant date fair value per share of options granted during the year ended December 31, 2022 and 2021 was $2.49 and $6.99, respectively. There were no options exercised during the year ended December 31, 2022. The intrinsic value of options exercised during the year ended December 31, 2021 was $0.2 million. As of December 31, 2022, total unrecognized compensation cost related to the unvested stock options was approximately $5.3 million, which is expected to be recognized over a weighted-average period of 2.4 years.

Stock-Based Compensation Expense

The following table presents the components and classification of stock-based compensation expense (in thousands):

	Year Ended December 31,	
	2022	2021
Research and development	$ 1,433	$ 1,237
General and administrative	1,767	1,580
Total stock-based compensation expense	$ 3,200	$ 2,817

No related income tax benefits were recorded during the years ended December 31, 2022 or 2021.

12. Net Loss per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows (in thousands, except share and per share amounts):

	Year Ended December 31,	
	2022	2021
Numerator:		
Net loss	$ (63,005)	$ (51,823)
Cumulative dividends on convertible preferred stock	—	(2,309)
Net loss attributable to common stockholders	$ (63,005)	$ (54,132)
Denominator:		
Weighted-average shares of common stock outstanding, basic and diluted	24,960,008	21,733,960
Net loss per share attributable to common stockholders, basic and diluted	$ (2.52)	$ (2.49)

The Company's potential dilutive securities have been excluded from the computation of diluted net loss per share attributable to common stockholders whenever the effect of including them would be to reduce the net loss per share. In periods where there is a net loss, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The following table sets forth the outstanding shares of common stock equivalents, presented based on amounts outstanding at each period end, that were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have been anti-dilutive:

	Year Ended December 31,	
	2022	2021
Outstanding stock options	3,476,377	3,037,463
Unvested restricted stock units	219,742	—
Unvested restricted stock awards	—	12,537
Total	3,696,119	3,050,000

13. License and Collaboration Agreement with Regeneron

Agreement Overview

In November 2017, the Company entered into the Regeneron Agreement. The Regeneron Agreement had an original research term of five years and granted Regeneron the right to extend the research term for up to two years in one-year intervals. In November 2021, Regeneron exercised its first option to extend the term of the research program through November 2023. Pursuant to the Regeneron Agreement, during the research term, the Company has established research plans that specify the activities each party undertakes with respect to the discovery or development of therapies directed to specific collaboration targets, which are referred to as collaboration products. Each party is responsible for its own respective costs and has agreed to use commercially reasonable efforts to complete the activities as designated in the agreed-upon research plan. Additional collaboration targets may be added to the Regeneron Agreement by mutual consent or if they arise from certain novel target identification activities conducted under the Regeneron Agreement and achieve mutually agreed validation criteria. The Company is primarily responsible for the direction and conduct of the research program. Regeneron is primarily responsible for the contribution of various technologies and expertise of its own as well as contribution of employees and research services. A joint research committee oversees the research program.

A joint product committee oversees development and commercialization of a collaboration product following IND acceptance for such collaboration product. As between the parties, the Company is solely responsible for developing and commercializing collaboration products in the field of hearing loss and balance disorders. The Company has an obligation to use commercially reasonable efforts to develop and commercialize such collaboration products in the field. During the term of the Regeneron Agreement, neither the Company nor Regeneron may develop or commercialize any products directed to collaboration targets in the field of treatment and prevention of disease involving loss of hearing or balance, other than pursuant to the Regeneron Agreement.

Pursuant to the Regeneron Agreement, Regeneron paid an upfront non-reimbursable fee of $25.0 million and purchased 12,500,000 shares of Series B Preferred Stock at price per share of $2.00 (see Note 10). If Regeneron elects to extend the term of the research program, it will be obligated to pay $10.0 million for each one-year extension. In addition to the upfront payment, the Company is eligible to receive additional milestones through a Phase 2 clinical trial of up to $35.5 million in the aggregate if the collaboration product is a biologic or up to $33.5 million in the aggregate if the collaboration product is a small molecule. Regeneron contributions are intended to reflect approximately half of the total costs needed to complete a Phase 2 clinical trial. From and after the initiation of a registration enabling trial, unless Regeneron decides to opt-out, the Company has agreed to split development and regulatory costs with Regeneron on an equal basis through the registration enabling trials.

Under the Regeneron Agreement, the Company is required to pay Regeneron tiered royalties on the worldwide net sales of collaboration products at percentages which range from mid-single digit to mid-thirties, with the exact royalty rate depending on the extent to which Regeneron shared in the funding of the collaboration product, the level of net sales of the collaboration product, the nature of any intellectual property contributed by Regeneron included in the collaboration product and whether the product is sold inside or outside the field as defined in the Regeneron Agreement.

Pursuant to the Regeneron Agreement, the Company has granted to Regeneron a right of first negotiation if it chooses to license or otherwise transfer rights to develop or commercialize collaboration products. Regeneron may opt-out of the collaboration with respect to any collaboration product (i) following submission of the IND to the FDA for a collaboration product, (ii) immediately prior to the initiation of a registration enabling trial, (iii) immediately prior to the submission of a marketing authorization application and (iv) at any time following the initiation of the registration enabling trial, upon notice to the Company within a specified time period. If Regeneron opts out with respect to a collaboration product, it does not owe further milestones on that collaboration product and will no longer share development expenses for such collaboration product. Regeneron may opt back into a collaboration product under certain circumstances.

The term of the Regeneron Agreement will continue until neither the Company nor any of its affiliates nor any of its sublicensees are developing or commercializing any collaboration products. Either party may terminate the agreement for cause for the other party's uncured material breach on prior written notice if the other party becomes insolvent or in certain circumstances in which either party challenges the patent rights of the other party.

In October 2020, the Company and Regeneron entered into an amendment to the Regeneron Agreement (the "First Amendment") pursuant to which, among other things, ATOH1, the target of the DB-ATO program, was removed as a collaboration target and the terms and plans for the DB-OTO and AAV.103 programs were modified. In connection with the First Amendment, the Company issued 10,000,000 shares of Series C Preferred Stock to Regeneron in consideration for its entry into the First Amendment. For the DB-OTO program, the Company also committed to utilize a specified level of research personnel in the program. In addition, upon certain suspensions of development activities for a specified period of time, or if the Company fails to invest specified levels of committed resources to the DB-OTO program, Regeneron would have certain remedies, including the ability to obtain control over further development and commercialization of DB-OTO and AAV.103, subject to payments to the Company to be negotiated, and the ability to terminate its obligations to the Company with respect to other collaboration products. Pursuant to the First Amendment, Regeneron agreed to pay the Company $0.3 million to fund the Company's ongoing research plan and $0.5 million to help secure the services of a contract development and manufacturing organization. The $0.5 million payment is creditable against the milestone associated with the initiation of manufacturing to support GLP toxicology studies of DB-OTO. Additionally, Regeneron agreed to reimburse the Company for up to $10.5 million of third-party costs related to IND-enabling studies for DB-OTO as such costs are incurred, and the Company agreed that the aggregate potential milestone payments for DB-OTO would be reduced by $15.0 million. In addition, for DB-ATO, the Company agreed to pay to Regeneron a royalty calculated as a low-to mid-single digit percentage of net sales of DB-ATO, on a country-by-country basis, until the latest of the expiration of the last patent covering DB-ATO in such country, the expiration of all applicable regulatory exclusivities for DB-ATO in such country and the tenth anniversary of the first commercial sale of DB-ATO in such country.

In November 2021, Regeneron elected to extend the research term of the collaboration. The research term was extended to November 15, 2023 and Regeneron paid the Company an extension fee of $10.0 million. As of December 31, 2022, there was no unbilled accounts receivable to the Company. As of December 31, 2021, the Company had an unbilled accounts receivable of $11.4 million related to the remaining balance of reimbursable third-party costs of $1.4 million for IND-enabling studies for DB-OTO and $10.0 million related to the extension fee resulting from Regeneron exercising its right to extend the research term. Through December 31, 2022, the Company had received an aggregate of $5.5 million in milestone payments from Regeneron pursuant to the collaboration. As of December 31, 2022, the next milestone that the Company was eligible to receive was in relation to the initiation of manufacturing for its AAV.103 program or the initiation of a Phase 1 clinical trial of DB-OTO. In February 2023, the Company entered into a second amendment to the Regeneron Agreement to provide for accelerated milestone payments by Regeneron to the Company for clinical development milestones for DB-OTO and pre-IND milestones for AAV.103 (see Note 17).

Accounting Analysis

Regeneron Agreement

The Company concluded that both the Company and Regeneron were active participants in future research and development activities under the Regeneron Agreement, and both parties were exposed to significant financial risks and rewards dependent on the commercial success of such activities. Further, the Company did not consider Regeneron to be a customer as Regeneron did not transact with the Company to obtain goods and services that were an output of the Company's ordinary activities in exchange for consideration. Specifically, in this transaction, Regeneron did not receive, and did not have an option to receive, a development and commercialization license from the Company for any collaboration products. Therefore, Regeneron did not have the right to develop and commercialize any of the intellectual property developed under the agreement. Because Regeneron was considered a collaborative partner that was subject to the significant risks and rewards under the agreement, the Company concluded the agreement was within the scope of ASC 808. The Company analogized to the guidance in ASC 606 to determine the measurement and recognition of the consideration received from Regeneron. By analogy to ASC 606, the Company identified its obligations to Regeneron (referred to as performance obligations under ASC 606), determined the amount of consideration to be recognized (referred to as the transaction price under ASC 606) and assessed the pattern of recognition. ASC 606 requires promised goods and services that are both (i) capable of being distinct and (ii) distinct within the context of the contract to be treated as separate performance obligations. Based on the Company's analysis, the Company's promised services consisted mainly of (i) research activities related to target discovery and (ii) performing research activities related to certain targets identified during the research program through the submission of an IND. All research activities were considered a single performance obligation because the research activities are interrelated and interdependent as many of the research activities performed benefited the targets. The goal of the parties was to develop as many targets as possible during the research program and therefore the Company's promised services were not distinct within the context of the contract. The transaction price consisted of the $25.0 million upfront payment. Future milestones, which would be considered variable consideration under ASC 606, were highly dependent on the success of the Company's early stage research activities and therefore were not included in the transaction price until such time as the achievement of such milestone was considered probable. The Company concluded that it satisfied its obligations under the agreement over time as Regeneron received the benefit of the research services as the services were performed. The Company concluded the most appropriate method to track progress towards completion of the performance obligation was an input method that was based on costs incurred.

The Company viewed the non-refundable upfront $25.0 million payment as reimbursement of the Company's costs under the agreement which were accounted for as research and development expenses in the Company's consolidated statement of operations and comprehensive loss. Further, while Regeneron is a related party (see Note 16), there was no presumption that the Company would reimburse Regeneron for the upfront payment as the amounts represented a reimbursement for research and development costs incurred and there were no terms or conditions that would require repayment. As such, the upfront payment is being recognized as a reduction to research and development expense (contra-research and development expense) in the Company's consolidated statements of operations and comprehensive loss based on the Company's progress towards completion of its research activities under the research plan.

Consideration to be received from Regeneron relating to the DB-OTO clinical development milestones will begin to be recognized over time once the achievement of each clinical development milestone is deemed probable. Consideration will be measured using an input method based on costs incurred to date relative to total cost. The Company's promised services are the development services under the development plan through a registration-enabling study or submission of a marketing authorization application. All development services are considered a single performance obligation being performed under the development plan. The Company will continue to monitor the likelihood of achievement of each clinical development milestone and will remove the respective constraints when achievement is deemed probable. The Company will recognize a cumulative catch-up adjustment when the constraint is removed, which will be calculated as the respective milestone payment multiplied by the measure of progress at that time.

First Amended Agreement

The Company concluded that both the Company and Regeneron remain active participants in the research and development activities under the First Amended Agreement, both parties remain exposed to significant financial risks and rewards dependent upon the commercial success of such activities, and Regeneron does not meet the definition of a customer under ASC 606. Specifically, Regeneron did not receive in the Amended Agreement, and continued to not have an option to receive, a development and commercialization license from the Company for any collaboration products. Therefore, Regeneron continues to not have the right to develop and commercialize any of the intellectual property developed under the Amended Agreement. Accordingly, the Company concluded the Amended Agreement is within the scope of ASC 808 and the Company continues to apply ASC 606 by analogy to account for the Amended Agreement.

As such, the Company analogized to the contract modification guidance in ASC 606 to account for the scope and pricing changes contained in the Amended Agreement. The Company concluded the performance obligation under the Amended Agreement, continues to be a single performance obligation and the remaining services under the Amended Agreement are not distinct from those already provided. Therefore, the Company accounted for the modification by updating the transaction price and measure of progress prospectively with a cumulative catch-up entry recorded as of the effective date of the Amended Agreement. As of December 31, 2022, the transaction price of $46.9 million consists of (i) $25.0 million received upfront, (ii) $0.3 million received to fund the ongoing research plan, (iii) $5.5 million of aggregate milestones achieved, (iv) $10.5 million in reimbursements for third-party costs related to IND-enabling studies for DB-OTO, and (v) $10.0 million as consideration for Regeneron's election to extend the research term, partially offset by the fair value of the Series C convertible preferred stock issued to Regeneron of approximately $4.4 million. The Company concluded the issuance of Series C Preferred Stock should be accounted for consistent with consideration paid to a customer and is therefore a reduction of the transaction price under the Amended Agreement.

The Company accounted for Regeneron's exercise of its right to extend the research term for an additional year as a contract modification. The extension did not change the scope of the Company's obligations under the Amended Agreement. The Company updated the transaction price to include the $10.0 million extension fee and measure of progress to reflect the extended research term. Following Regeneron's extension in November 2021, the updated transaction price under the collaboration is $46.9 million. Future milestones continue to be fully constrained until such time as the achievement of such milestones are considered probable.

The Company concluded that it continues to satisfy its obligations over time as Regeneron receives the benefit of the research services as the services are performed and the most appropriate method to track progress towards completion of the performance obligation is an input method that is based on costs incurred.

There are significant judgments and estimates inherent in the determination of the costs to be incurred for the research and development activities related to the collaboration with Regeneron. These estimates and assumptions include a number of objective and subjective factors, including the likelihood that a target will be successfully developed through its IND filing and the estimated costs associated with such development, including the potential third-party costs related to each target's IND-enabling study.

The Company recognized $8.4 million and $11.0 million of contra-research and development expense for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022 and 2021, there was $9.4 million and $8.1 million of deferred collaboration liability classified in current liabilities, respectively, and $6.8 million and $16.4 million of deferred collaboration liability classified in long-term liabilities, respectively.

14. Employee Retirement/Savings Plan

The Company maintains an employee retirement/savings plan (the "Retirement Plan") that permits participants to make tax-deferred contributions by salary reduction pursuant to Section 401(k) of the Internal Revenue Code. For the years ended December 31, 2022 and 2021 the Company provided a matching contribution to the Retirement Plan based on a match formula of 100% up to 3%, and 50% of the next 2% or a maximum match of 4%. The Company made matching contributions of $0.5 million and $0.3 million for the years ended December 31, 2022 and 2021, respectively.

15. Income Taxes

During the year ended December 31, 2022, the Company recorded $0.2 million of income tax expense, primarily related to the recording of income tax expense for the Company's Australian subsidiary. During the year ended December 31, 2021, the Company recorded $1.8 million of income tax expense, which was primarily driven by the recording of an uncertain tax position and additional income tax expense for the Australian subsidiary. For financial reporting purposes, loss before provision for income taxes, includes the following components (in thousands):

	Year Ended December 31,	
	2022	2021
Domestic	$ (62,859)	$ (50,825)
Foreign	94	799
Loss before income taxes	$ (62,765)	$ (50,026)

The provision (benefit) for income taxes consists of the following (in thousands):

	Year Ended December 31,	
	2022	2021
Current:		
Federal	$ —	$ —
State	13	—
Foreign	227	1,797
Total Current	240	1,797
Deferred:		
Federal	—	—
State	—	—
Foreign	—	—
Total Deferred	—	—
Loss before income taxes	$ 240	$ 1,797

A reconciliation of the expected income tax (benefit) computed using the federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,	
	2022	2021
Expected income tax benefit at the federal statutory rate	21.0%	21.0%
State taxes, net	5.9	5.8
Foreign taxes	—	(0.5)
Change in valuation allowance	(28.6)	(27.2)
Research and development tax credits	3.2	0.7
Rate differential on foreign operations	—	(0.1)
Stock compensation	(0.9)	(0.5)
Uncertain Tax Position	—	(2.9)
Permanent differences	(0.5)	0.1
Other	(0.5)	—
Effective income tax rate	(0.4)%	(3.6)%

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets and liabilities consisted of the following (in thousands):

	December 31,	
	2022	2021
Deferred tax assets:		
Federal, state and foreign net operating loss carryforwards	$ 59,068	$ 53,075
Research and development and other credits	3,835	1,840
Lease liability	3,800	—
Capitalized research and development expenses	9,998	—
Deferred rent and lease incentive obligation	—	1,321
Accrued expenses and other	1,428	1,551
Total gross deferred tax assets	78,129	57,787
Valuation allowance	(74,926)	(57,013)
Total deferred tax assets	$ 3,203	$ 774
Deferred tax liabilities:		
Right of use assets	(2,679)	—
Depreciation of fixed assets	(524)	(774)
Total deferred tax liabilities	$ (3,203)	$ (774)
Net deferred taxes	$ —	$ —

The Company evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets as of December 31, 2022 and 2021. Management considered the Company's cumulative net losses and concluded as of December 31, 2022 and 2021 that it was more likely than not that the Company would not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance was established against the net deferred tax assets as of December 31, 2022 and 2021.

Changes in the valuation allowance for deferred tax assets were as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Valuation allowance at beginning of the year	$ 57,013	$ 44,305
Increases recorded to income tax provision	17,913	12,708
Valuation allowance at end of year	$ 74,926	$ 57,013

Subject to the limitations described below, as of December 31, 2022 and 2021, the Company had U.S. federal net operating loss carryforwards of approximately $217.9 million and $196.3 million, respectively, to offset future federal taxable income. Federal net operating losses of $41.7 million will expire beginning in 2033. As of December 31, 2022, the Company had net operating losses of $176.2 million which had an indefinite life. As of December 31, 2022 and 2021, the Company had state net operating loss carryforwards of approximately $210.5 million and $187.9 million, respectively, to offset future state taxable income, which will begin to expire in 2035.

Subject to the limitations described below, at December 31, 2022 and 2021, the Company had federal research and development tax credit carryforwards of $1.9 million and $1.2 million, respectively, which expire beginning in 2033. The Company also had $1.3 million of Orphan Drug credit carryforwards, which expire beginning in 2043. As of December 31, 2022 and 2021, the Company had state research and development tax credit carryforwards of $0.9 million and $0.8 million, respectively, which expire beginning in 2032. The Company has generated federal and state research and development credits but has not conducted a study to document the qualified activity. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed, and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

Under the provisions of the Internal Revenue Code, the net operating loss and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service ("IRS") and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, 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 conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382 of the Internal Revenue Code, at any time since inception, utilization of the net operating loss carryforwards or research and development tax credit carryforwards would be subject to an annual limitation under Section 382 of the Internal Revenue Code, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term-tax-exempt rate, and then could be subject to additional adjustments, as required. Any limitations may result in expiration of a portion of the net operating loss carryforwards or research and development tax credit carryforwards before utilization. Further, until a study is completed by the Company and any limitation is known, no amounts are being presented as an uncertain tax position.

We assess the impact of various tax reform proposals and modifications to existing tax treaties in all jurisdictions where we have operations to determine the potential effect on our business and any assumptions we have made about our future taxable income. We cannot predict whether any specific proposals will be enacted, the terms of any such proposals or what effect, if any, such proposals would have on our business if they were to be enacted. Beginning in 2022, the Tax Cuts and Jobs Act of 2017 eliminates the currently available option to deduct research and development expenditures and requires taxpayers to amortize them over five years. The U.S. Congress is considering legislation that would defer the amortization requirement to future periods, however, we have no assurance that the provision will be repealed or otherwise modified.

The Company files income tax returns in the United States, Australia and Massachusetts. The statute of limitations for assessment by the IRS and state tax authorities is closed prior to 2018, although carryforward attributes that were generated prior to tax year 2019 may still be adjusted upon examination by the IRS or state tax authorities if they either have been or will be used in a future period. The Company is currently not under examination by the IRS or any other jurisdictions for any tax years. The statute of limitations for assessment by the Australian Taxation Office is four years from the date of return filing. The Company is not currently under examination by the Australian Taxation Office for any tax years.

The Company establishes reserves for uncertain tax positions based on management's assessment of exposures associated with tax positions taken on tax return filings. The tax reserves are analyzed periodically, and adjustments are made as events occur to warrant adjustments to the reserve.

As of December 31, 2022, the Company had $1.6 million of gross unrecognized tax benefits, of which $1.4 million would affect income tax expense if recognized, before consideration of the Company's valuation allowance. As of December 31, 2022, the gross unrecognized tax benefits included $0.2 million of deferred tax asset previously offset by a full valuation allowance. The Company does not expect the unrecognized tax benefits to change significantly over the next 12 months. The Company recognizes both interest and penalties associated with uncertain tax positions as a component of income tax expense. The Company has accrued penalties and provisions for interest of $0.5 million and $0.4 million as of December 21, 2022 and 2021, respectively.

A reconciliation of the gross unrecognized tax benefits are as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Unrecognized tax benefits at the beginning of the period	$ 2,084	$ —
Increases for current tax positions	—	2,084
Reductions related to previous tax positions	(85)	—
Reductions related to translation adjustments	(369)	—
Unrecognized tax benefits at the end of the period	$ 1,630	$ 2,084

16. Related Party Transactions

As of December 31, 2022, Regeneron held 2,097,314 shares of common stock, approximately 8.4% of common stock outstanding as of that date. During the years ended December 31, 2022 and 2021, the Company recognized $8.4 million and $11.0 million as a reduction to research and development expense (contra-research and development) based on progress towards completion of its research activities under the research plan for its license and collaboration agreement with Regeneron in its consolidated statements of operations and comprehensive loss. As of December 31, 2022, the Company had no unbilled accounts receivables due from Regeneron. As of December 31, 2021, the Company had $11.4 million of unbilled accounts receivables due from Regeneron (see Note 13). As of December 31, 2022 and 2021, the Company did not have any amounts due to Regeneron.

For the years ended December 31, 2022 and 2021, the Company recorded no expenses and $0.2 million of expenses, respectively, relating to consulting services provided by an entity affiliated with a stockholder of the Company and a member of the Company's Board of Directors. The Company terminated this arrangement effective December 31, 2021. As of December 31, 2022, the Company had no further amounts due to this entity. As of December 31, 2021, the Company had $0.2 million due to this entity, which was subsequently paid during the three months ended March 31, 2022.

17. Subsequent Events

The Company considers events and transactions that occur after the balance sheet date but prior to the issuance of the consolidated financial statements for potential recognition or disclosure in the consolidated financial statements.

In February 2023, the Company entered into a second amendment with Regeneron to provide for accelerated development milestone payments by Regeneron to the Company for clinical development milestones for DB-OTO and pre-IND milestones for AAV.103.

Subsequent to December 31, 2022, the Company issued and sold a total of 50,482 shares under the Sales Agreement for aggregate net proceeds of $0.2 million after deducting commissions payable by the Company.

On Friday, March 10, 2023, the Federal Deposit Insurance Corporation ("FDIC") announced that Silicon Valley Bank ("SVB") was closed and that the FDIC was appointed as receiver. As of March 10, 2023, the Company had three cash deposit accounts at SVB, each with a balance less than or equal to $250,000. The Company also had, as of March 10, 2023, approximately $4.0 million in a money market account at a separate independent financial institution for which SVB acted solely as custodian. The Company's other cash resources are held in custody accounts at separate independent financial institutions. On Sunday March 12, 2023, the Secretary of the Treasury, the Federal Reserve Board Chair and the FDIC Chairman issued a joint statement announcing the approval of actions enabling the FDIC to complete its resolution of SVB in a manner that fully protects all depositors. The Company will continue to monitor this evolving situation and is evaluating alternative commercial banking options.

[THIS PAGE INTENTIONALLY LEFT BLANK]

[THIS PAGE INTENTIONALLY LEFT BLANK]

Board of Directors

Laurence Reid, Ph.D.
President and Chief Executive Officer, Decibel Therapeutics, Inc.

William H. Carson, M.D.
Former President and Chief Executive Officer, Otsuka Pharmaceutical Development & Commercialization, Inc.

Neil Exter, M.B.A.
Partner, Third Rock Ventures

Alison Finger, M.B.A.
Former Chief Commercial Officer, bluebird bio, Inc.

Matthew Kapusta, M.B.A.
Chief Executive Officer, uniQure N.V.

Kevin McLaughlin, M.B.A.
Former Senior Vice President, Chief Financial Officer and Treasurer, Acceleron Pharma Inc.

Saraswathy Nochur, Ph.D.
Chief Diversity, Equity & Inclusion Officer, Alnylam Pharmaceuticals, Inc.

Peter A. Thompson, M.D.
Partner, OrbiMed Advisors LLC

Executive Officers

Laurence Reid, Ph.D.
President and Chief Executive Officer

James Murphy
Interim Chief Financial Officer

John Lee
Executive Vice President, Chief Development Officer

Anna Trask
Executive Vice President, Chief People Officer

Stock Listing

Our common stock is traded on the Nasdaq Global Select Market under the symbol “DBTX”.

Investor Information

Stockholders may request information about Decibel Therapeutics, Inc. by contacting us at 1325 Boylston Street, Suite 500, Boston, MA 02215, Attention: Decibel Investor Relations (Telephone: (617) 370-8701; Email: info@decibeltx.com). Information of interest to stockholders and investors, such as our annual reports, quarterly reports, proxy statements, press releases, and other information, is available on our website at www.decibeltx.com under “Investors.”

Annual Meeting

The annual meeting of stockholders will be held virtually via the Internet at the time and website stated below.

Tuesday, June 13, 2023
10:00 a.m. ET

www.proxydocs.com/DBTX

Corporate Counsel

Wilmer Cutler Pickering Hale and Dorr LLP
Boston, Massachusetts

Independent Registered Public Accounting Firm

Ernst & Young LLP
Boston, Massachusetts

Transfer Agent and Registrar

The transfer agent is responsible, among other things, for handling stockholder questions regarding lost stock certificates, address changes, including duplicate mailings and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address:

Computershare Trust Company, N.A.
150 Royall Street
Canton, MA 02021
www.computershare.com/us

Decibel Therapeutics, Inc.
1325 Boylston Street, Suite 500
Boston, Massachusetts
(617) 370-8701
Email: info@decibeltx.com

www.decibeltx.com