AVROBIO

What if ONE GENE can change your life?

Arianna, living with Gaucher disease

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

☐ **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 001-38537

AVROBIO, INC.

(Exact name of registrant as specified in its charter)

Delaware **(State or other jurisdiction of incorporation or organization)**	**81-0710585** **(I.R.S. Employer Identification No.)**
100 Technology Square **Sixth Floor** **Cambridge, Massachusetts** **(Address of principal executive offices)**	**02139** **(Zip Code)**

(617) 914-8420
(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**AVRO**	**Nasdaq Global Select Market**

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

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

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

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

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

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

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

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

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

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

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $34,838,485 as of June 30, 2022 (based on a closing price of $0.92 share as quoted by the Nasdaq Global Select Market as of such date). In determining the market value of non-affiliate common stock, shares of the registrant's common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The registrant had 44,088,283 shares of Common Stock, $0.0001 par value per share, outstanding as of March 16, 2023.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2023 annual meeting of shareholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2022. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

AVROBIO, Inc.
Annual Report on Form 10-K for the Fiscal Year Ended December 31, 2022
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Summary Risk Factors

Our business is subject to numerous risks and uncertainties that you should be aware of in evaluating our business. These risks include, but are not limited to, the following:

- We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability, and substantial doubt about our ability to continue as a going concern may create negative reactions to the price of our common stock.
- We will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.
- Our term loan agreement contains restrictions that potentially limit our flexibility in operating our business, and we may be required to make a prepayment or repay our outstanding indebtedness earlier than we expect. In addition, as a result of the deprioritization of our Fabry program in January of 2022, we can no longer draw $20.0 million of term loans that were contingent upon the achievement of certain milestones related to our development of AVR-RD-01 for Fabry disease.
- Business interruptions resulting from the coronavirus disease, or COVID-19, pandemic or similar public health crises have caused and may cause a disruption of the development of our product candidates and adversely impact our business.
- Our hematopoietic stem cell or HSC gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.
- Our product candidates and 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.
- Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.
- We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.
- We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.
- Even if we complete the necessary preclinical and clinical studies, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate and the approval may be for a narrower indication than anticipated.
- Only one of our clinical trials utilizes our plato® platform.
- We face significant competition in our industry and there can be no assurance that our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.
- Gene therapies are novel, complex and difficult to manufacture. We could experience production problems that result in delays in our development or commercialization programs or otherwise adversely affect our business.
- We expect to rely on third parties to conduct some or all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.
- We currently rely, and expect to continue to rely, on sole source suppliers for our automated, closed cell processing system; vector supply; plasmid supply; cell culture media supply; and drug product manufacturing. In addition, we are dependent on a limited number of suppliers for some of our other components and materials used in our product candidates.
- Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

- Our rights to develop and commercialize our product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.
- If we experience material weaknesses or deficiencies in the future or otherwise fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our stock price.
- Our failure to meet Nasdaq Global Select Market's or Nasdaq's, continued listing requirements could result in a delisting of our common stock.

The summary risk factors described above should be read together with the text of the full risk factors below, in the section entitled "Risk Factors" and the other information set forth in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes, as well as in other documents that we file with the Securities and Exchange Commission, or the SEC. The risks summarized above or described in full below are not the only risks that we face. Additional risks and uncertainties not precisely known to us, or that we currently deem to be immaterial may also materially adversely affect our business, financial condition, results of operations and future growth prospects.

Forward-looking Information

This Annual Report on Form 10-K contains forward-looking statements which are made pursuant to the safe harbor provisions of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements may be identified by such forward-looking terminology as "aims," "anticipates," "believes," "continue," "could," "designed to," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "predicts," "projects," "seeks," "strives," "should," "will," and similar expressions or the negative of these terms. Our forward-looking statements are based on a series of expectations, assumptions, estimates and projections about our company, are not guarantees of future results or performance and involve substantial risks and uncertainty. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements. Our business and our forward-looking statements involve substantial known and unknown risks and uncertainties, including the risks and uncertainties inherent in our statements regarding:

- the impact of the COVID-19 pandemic or any other public health crisis on our clinical trial programs, clinical supply and business generally;
- the timing, progress and results of preclinical studies and clinical trials for our programs and product candidates, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the existence or absence of side effects or other properties relating to our product candidates which could delay or prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences following any potential marketing approval;
- the durability of effects from our product candidates;
- the timing, scope or likelihood of regulatory filings and approvals;
- the anticipated regulatory pathway for our product candidates and planned interactions with regulatory agencies;
- our ability to develop and advance product candidates into, and successfully complete, clinical studies;
- our expectations regarding the size of the patient populations for our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, product candidates, technology and plato platform;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our product candidates, if approved;
- the scalability and commercial viability of our manufacturing methods and processes, including our move to a closed, automated system;

- the rate and degree of market acceptance and clinical utility of our product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- our plans and expectations regarding our efforts to evaluate strategic opportunities with respect to one or more of our programs, our technology or our plato platform;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our current and future product candidates, as well as any statements as to whether we do or do not infringe, misappropriate or otherwise violate any third-party intellectual property rights;
- our financial performance;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- developments and projections relating to our competitors and our industry, including other lentiviral or HSC gene therapy companies;
- our expectations related to the use of our cash reserves;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to comply with the terms of our term loan agreement;
- our ability to avoid any findings of material weaknesses or significant deficiencies in the future;
- our ability to satisfy the continued listing requirements of the Nasdaq, including a minimum bid price, and to maintain our common stock listing on Nasdaq or any stock exchange;
- the impact of laws and regulations, including without limitation recently enacted tax reform legislation;
- our expectations regarding the time during which we are an emerging growth company under the Jumpstart Our Business Startups Act of 2012, or JOBS Act; and
- other risks and uncertainties, including those listed under the caption “Risk Factors.”

All of our forward-looking statements are as of the date of this Annual Report on Form 10-K only. In each case, actual results may differ materially from such forward-looking information. We can give no assurance that such expectations or forward-looking statements will prove to be correct. An occurrence of or any material adverse change in one or more of the risk factors or risks and uncertainties referred to in this Annual Report on Form 10-K or included in our other public disclosures or our other periodic reports or other documents or filings filed with or furnished to the SEC could materially and adversely affect our business, prospects, financial condition and results of operations. Except as required by law, we do not undertake or plan to update or revise any such forward-looking statements to reflect actual results, changes in plans, assumptions, estimates or projections or other circumstances affecting such forward-looking statements occurring after the date of this Annual Report on Form 10-K, even if such results, changes or circumstances make it clear that any forward-looking information will not be realized. Any public statements or disclosures by us following this Annual Report on Form 10-K that modify or impact any of the forward-looking statements contained in this Annual Report on Form 10-K will be deemed to modify or supersede such statements in this Annual Report on Form 10-K.

Note Regarding Trademarks

All brand names or trademarks appearing in this report are the property of their respective holders.

PART I

Unless the context requires otherwise, references in this Annual Report on Form 10-K to the "Company," "AVROBIO," "we," "us," and "our" refer to AVROBIO, Inc. Our "board of directors" refers to the board of directors of AVROBIO, Inc.

Item 1. Business.

Overview

We are a clinical-stage gene therapy company with a purpose to free people from a lifetime of genetic disease. Our company is focused on developing potentially curative hematopoietic stem cell, or HSC, gene therapies to treat patients with rare diseases following a single dose treatment regimen. Our gene therapies employ HSCs that are harvested from the patient and then modified with a lentiviral vector to insert the equivalent of a functional copy of the gene that is mutated in the target disease. We believe that our approach, which is designed to transform hematopoietic stem cells from patients into therapeutic products, has the potential to provide curative benefit for a range of diseases. Our initial focus is on a group of rare genetic diseases referred to as lysosomal disorders, some of which today are primarily managed with enzyme replacement therapies, or ERTs. These lysosomal disorders have well-understood biologies, identified patient populations, established standards of care yet with significant unmet needs, and represent large market opportunities with approximately $3.5 billion in worldwide net sales in 2022.

Our pipeline is currently comprised of four HSC gene therapy programs: AVR-RD-02 for the treatment of Gaucher disease type 1 and type 3; AVR-RD-04 for the treatment of cystinosis; AVR-RD-05 for the treatment of neuronopathic mucopolysaccharidosis type II, or MPS-II or Hunter syndrome; and AVR-RD-03 for the treatment of Pompe disease.

AVR-RD-02 is currently being studied for the treatment of Gaucher disease type 1 in a Company-sponsored Phase 1/2 clinical trial, which we refer to as the Guard1 clinical trial. Four patients have been dosed to date in the Guard1 clinical trial, and we have enrolled six patients to date. We are actively recruiting additional potential patients for our currently active sites. We provided updated interim clinical trial data on December 7, 2022, at which time we also provided an update on discussions with regulatory authorities regarding Gaucher disease type 3, including our plans for further clinical development. Following positive feedback from the U.S. Food and Drug Administration, or FDA, and the U.K. Medicines and Healthcare products Regulatory Agency, or MHRA, we are now planning for the initiation of a registrational, global Phase 2/3 clinical trial for Gaucher disease type 3 (GD3) in the second half of 2023, subject to regulatory alignment.

In October 2022, the FDA granted rare pediatric disease designation, or RPDD, for AVR-RD-02 for the treatment of Gaucher disease. Under this program, if AVR-RD-02 is approved by FDA, then the Company may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product candidate. That same month, AVR-RD-02 also was granted an Innovation Passport under the Innovative Licensing and Access Pathway, or ILAP, from the MHRA. ILAP designation is intended to accelerate the regulatory review process and facilitate patient access in the U.K. for seriously debilitating and life-threatening diseases. AVR-RD-02 previously received Fast Track Designation from the FDA in December 2021 and orphan drug designation, or ODD, in the U.S. in September 2019 and in the European Union, or EU, in September 2020.

AVR-RD-04 is currently being studied for the treatment of cystinosis by our collaborators at the University of California, San Diego, or UCSD, in a Phase 1/2 collaborator-sponsored clinical trial. Enrollment of this clinical trial is complete with a total of six patients dosed. In May 2022, our collaborators at UCSD reported updated interim data from the Phase 1/2 collaborator-sponsored clinical trial of AVR-RD-04 at the 25th Annual Meeting of American Society for Gene and Cell Therapy, or ASGCT, in Washington, D.C. and at the 19th annual WORLD*Symposium* in Orlando, Florida on February 25, 2023. In the first quarter of 2023, we completed a scientific advice meeting with MHRA and received feedback from the FDA regarding a planned Company-sponsored clinical trial for AVR-RD-04. Based on these regulatory interactions and feedback, we are planning to initiate activities for a Company-sponsored Phase 1/2 clinical trial in the second half of 2023, which is designed to be registration-enabling. Clinical sites are anticipated in the United Kingdom, Europe and the United States. Our current plan involves a two-part clinical development strategy, including both a pre-renal transplant population clinical trial and a post-renal transplant population. We expect to provide clinical and regulatory updates on the Phase 1/2 clinical trial of AVR-RD-04 at ASGCT in May 2023.

In September 2022, the FDA granted RPDD for AVR-RD-04 for the treatment of cystinosis. AVR-RD-04 has previously received Fast Track Designation from the FDA and ODD from the FDA and EMA.

AVR-RD-05 is our preclinical program for the treatment of Hunter syndrome. In September 2022, we announced that the MHRA, Research Ethics Committee, or REC, and Health Research Authority, or HRA, have accepted the clinical trial

application, or CTA, submitted by our collaborators at The University of Manchester for initiation of a Phase 1/2 collaborator-sponsored clinical trial of investigational autologous HSC gene therapy in infants diagnosed with MPS-II, or Hunter Syndrome, in the United Kingdom. We currently expect the Phase 1/2 collaborator-sponsored clinical trial will be initiated in 2023. In October 2021, the FDA granted RPDD for AVR-RD-05 for the treatment of Hunter syndrome. The FDA previously granted ODD for AVR-RD-05.

AVR-RD-03 is our preclinical program for the treatment of Pompe disease. While we continue to advance AVR-RD-03, we are prioritizing our Gaucher disease and cystinosis clinical programs. As a result, we no longer expect to initiate a clinical trial for AVR-RD-03 in 2023.

In January 2022, we announced the deprioritization of AVR-RD-01, our investigational gene therapy program for Fabry disease. This decision was made due to several factors, including new clinical data showing variable engraftment patterns from the five most recently dosed patients in the Company's Phase 2 clinical trial of AVR-RD-01 for the treatment of Fabry disease, which we refer to as the FAB-GT clinical trial. The emergence of such new data would have significantly extended the program's development timeline. That development, coupled with an increasingly challenging market and regulatory environment for Fabry disease, were among the primary factors leading to the Company's deprioritization of its Fabry program. As a result of the deprioritization, the Company stopped enrollment of its Phase 2 FAB-GT clinical trial and since early 2022, we have been focusing on our other pipeline programs.

Since its first clinical use in 2003, HSC gene therapy has been studied in several third parties' clinical trials for rare diseases such as transfusion-dependent beta thalassemia, cerebral adrenoleukodystrophy, metachromatic leukodystrophy, and adenosine deaminase severe combined immunodeficiency. Initially, the use of HSC gene therapies was restricted primarily to the most severe diseases where the risks of the typical requirement for ablating the patients' bone marrow had a clinically justifiable risk/benefit profile. To date, hundreds of patients have been treated with HSC gene therapies in third parties' and our rare disease clinical trials, and we believe the technology can be developed for other serious conditions based on a rigorous risk/benefit assessment.

The myeloablation procedure, also known as the conditioning regimen, is typically an essential step in the *ex vivo* gene therapy treatment procedure and is administered prior to the gene therapy. We have worked to optimize the conditioning regimen through utilization of a precision busulfan dosing program, which we refer to as Target Concentration Intervention, or TCI. TCI is designed to enable careful titrating of exposure to the conditioning drug to a specific area under the curve, or AuC. The conditioning regimen utilized as part of our plato platform includes TCI to assess how rapidly the individual patient metabolizes the conditioning agent so physicians can adjust the dose as needed, with a goal of minimizing side effects from conditioning while maximizing the potential of durable engraftment. In addition, we are evaluating the potential future use of alternative conditioning agents in lieu of the current busulfan TCI conditioning regimen. For example, we have entered into a collaboration agreement with Jasper Therapeutics, Inc. and are currently evaluating the potential use of its monoclonal antibody conditioning agent. We are also evaluating the potential use of additional agents to tailor the conditioning regimen for certain disease indications.

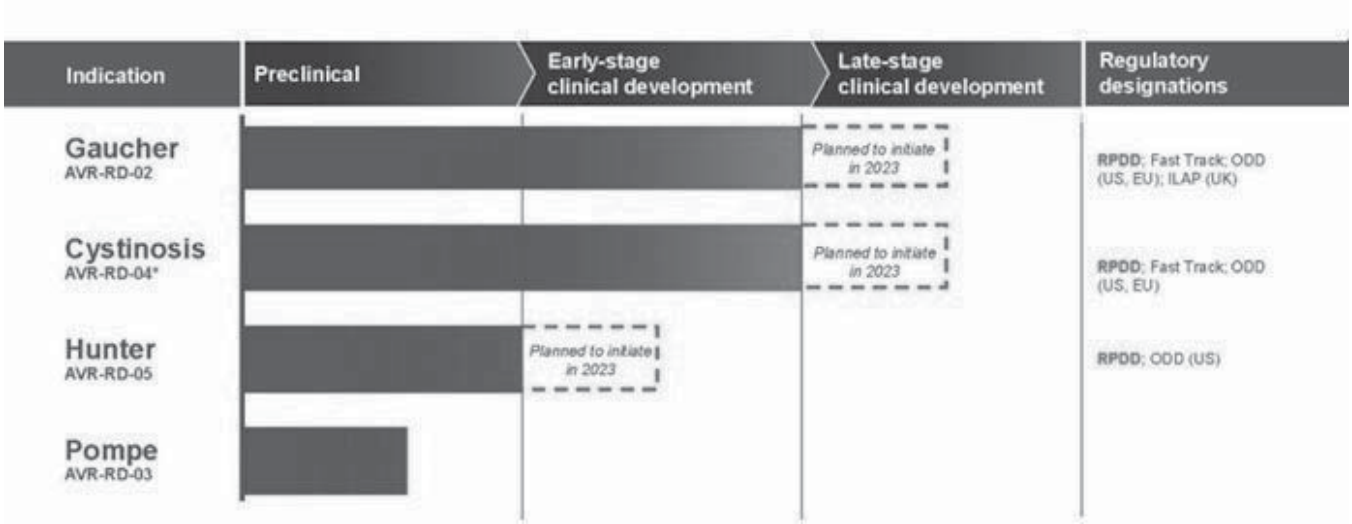
plato® is our gene therapy platform designed to provide the foundation for the potential worldwide commercialization of our gene therapies, if approved. It is a HSC gene therapy platform incorporating multiple upgrades including a four-plasmid lentiviral vector designed to optimize vector copy number; transduction efficiency and resulting enzyme activity; a closed, automated manufacturing system designed to improve consistency and predictability of the drug product; and a personalized approach to conditioning. Six patients in our FAB-GT clinical trial of AVR-RD-01, for which enrollment was halted, and four patients in our Guard1 clinical trial of AVR-RD-02 have been dosed with drug product manufactured utilizing the plato platform, and we intend to utilize the plato platform with these process changes for all future patients enrolling in our Company-sponsored clinical trials. We believe our innovations in viral vector design, cellular manufacturing, cryopreservation, conditioning and other related processes are important steps towards advancing the field of HSC gene therapy and realizing its full potential to treat a number of diseases. We plan to continue leveraging advancements in stem cell transplantation with the goal of improving patient tolerability of our HSC gene therapies.

Our gene therapies currently target rare lysosomal disorders in which the current standard of care provides the mechanistic proof that the enzymes or proteins produced endogenously following treatment with our gene therapies can offer benefit to patients. Typically, in lysosomal disorders, a gene mutation results in the deficiency or malfunctioning of an enzyme or other protein. This results in the inability of lysosomes to properly process cellular materials such as damaged organelles. As a result, substrates and their metabolites accumulate to toxic levels in the body's cells and, in turn, disrupt the function of multiple tissues and organs. Gaucher disease (types 1 and 3), Hunter syndrome and Pompe disease are currently primarily managed by bi-weekly (or weekly in the case of Hunter syndrome), multi-hour infusions with ERTs that seek to

exogenously replace the missing functional enzyme. However, given their pharmacokinetics, most ERTs typically remain in the plasma only for a short period of time and thus are not ideal because they are only dosed weekly or every two weeks. Cystinosis is currently treated with two oral formulations of cysteamine that must be taken orally every 12 or 6 hours, leading to significant pill burden and compliance challenges. Further, oral cysteamine treatment has no effect on ocular cystine crystals deposits, thus requiring patients to be treated with topical cysteamine eye drops which must be applied each hour the patient is awake. These existing therapies manage, rather than cure, the underlying diseases and, as a result, patients continue to have disease progression. Further, the frequent, periodic and life-long dosing schedule required for ERTs and cysteamine results in significant costs for the healthcare system and is burdensome for the patient.

We believe our gene therapies leverage the well-understood mechanism of ERTs by transforming a patient's own stem cells into a drug product that enables the patient to express functional enzyme or other protein and mirror the biology seen in an otherwise healthy individual. We believe that a single dose of our gene therapies may provide meaningful life-long benefit to these patients and potentially halt the progression of these diseases while also potentially providing significant health economic advantages.

Our programs leverage years of extensive preclinical and early clinical research by leading researchers, as well as our internal research and ongoing clinical efforts. The status of our HSC gene therapy programs is reflected below.



*Planned regulatory milestones subject to regulatory agency clearance; *Collaborator-sponsored Phase 1/2 clinical trial of AVR-RD-04 is funded in part by grants to UCSD from the California Institute for Regenerative Medicine (CIRM), Cystinosis Research Foundation (CRF), and National Institutes of Health (NIH).*

Our Expertise

We are led by biopharmaceutical experts with extensive experience in gene and cellular therapy, and rare diseases. Our team has broad expertise in the clinical and regulatory aspects of rare diseases as well as process development and manufacturing for cellular therapies. Members of our management team have held senior positions at Affinia Therapeutics, Amicus Therapeutics, Biogen, GlaxoSmithKline, Lentigen Technology, Novartis, Takeda, Spark Therapeutics, and other companies pursuing development, manufacturing and commercialization of gene, cellular and other therapies to treat rare diseases.

Our Strategy

Our purpose is to develop and commercialize HSC gene therapies that free patients from a lifetime of genetic disease. Key elements of our strategy include:

- *Advance our pipeline targeting lysosomal disorders.* We are developing a pipeline of four gene therapies to treat Gaucher disease (type 1 and type 3), cystinosis, Hunter syndrome and Pompe disease. We intend to continue to advance these programs in parallel and to obtain clinical data that could potentially support regulatory filings around the world.
- *Leverage our proprietary plato® gene therapy platform to accelerate development of our pipeline.* Continue implementing and enhancing our plato platform covering vector design and production, drug product manufacturing, as well as analytics. We believe our end-to-end plato platform is scalable for planned global

commercialization, if approved. We believe our innovations in viral vector design, cellular manufacturing, cryopreservation, and other related processes are important steps towards advancing the field of HSC gene therapy and realizing its full potential to treat a number of diseases. plato incorporates a four-plasmid lentiviral vector designed to optimize vector copy number, transduction efficiency and resulting enzyme activity. In combination with this vector, in some indications we use a number of proprietary peptide tag technologies to enhance uptake of therapeutic protein in key tissues. We have also developed a manufacturing process that we believe is both reproducible and scalable, and we believe this technology could enable us to deliver our gene therapies to patients, if approved, in quantities sufficient for global commercial supply. In addition, we believe our personalized approach to conditioning using busulfan through TCI could enable us to deliver durable, "head-to-toe" treatment of symptoms and early intervention in the treatment of lysosomal disorders. We intend to continue to leverage advancements in stem cell transplantation, including evaluating the potential use of monoclonal antibody conditioning.

- *Leverage our approach beyond our initial indications.* We are developing gene therapies for the treatment of four different lysosomal disorders and believe that we will gain significant learnings and technical insights from these programs. In the future, we may leverage our technology and insights to treat a number of rare and non-rare diseases where we believe our HSC approach has transformative potential.
- *Selectively and opportunistically evaluate opportunities and initiatives to maximize business value.* As part of our business strategy, from time to time, we evaluate and intend to continue to evaluate opportunities to collaborate, partner, enter into joint ventures or undertake other strategic initiatives with third parties with respect to one or more of our programs, our technology or our plato platform, all with the goal of maximizing the value of our business. Despite devoting significant efforts to identify and evaluate potential opportunities, there can be no assurance that efforts will result in us pursuing any transaction or that any transaction, if pursued, will be completed on attractive terms or at all.

Our Approach

We develop gene therapies utilizing our HSC-based approach to transform a patient's own stem cells into a drug product. Our investigational gene therapies employ lentiviral vectors that are designed to result in stable integration of the desired genes in the chromosomes of HSCs such that they are permanently maintained in the cell and can be reproduced as the cell divides. HSCs are primitive stem cells that develop into all types of blood cells, including white blood cells, red blood cells and platelets. To accomplish this, we harvest a patient's HSCs and modify them *ex vivo* to add the equivalent of a functional copy of the gene that is mutated in the target disease. We then infuse the genetically modified cells back into the patient. Our gene therapies are designed to be administered to the patient as a one-time therapy following a conditioning regimen.

We are focused on employing our approach to treat and potentially cure lysosomal disorders. These disorders have well-understood biologies, identified patient populations, established standards of care that leave many patients with significant unmet medical needs, and represent large markets with approximately $3.5 billion in worldwide net sales in 2022. We believe our HSC gene therapy approach can be industrialized into a robust, scalable and, if approved, commercially viable process that will allow us to deliver our potentially curative therapies to patients across the world.

Potential Advantages of HSC Gene Therapy Approach

We believe HSC gene therapy has the potential to provide numerous advantages, including:

- *Durable benefit.* We believe HSC gene therapy has the potential to provide life-long benefits with a single dose. Lentiviral vectors can integrate stably into the genome of HSCs and, when these cells replicate, they pass the integrated genes on to their progeny cells. Across the industry, efficacy in patients treated with HSC gene therapies have been demonstrated for longer than 13 years.
- *Systemic therapeutic effect.* Progeny cells circulate systemically and may migrate into tissues and therefore have the ability to provide therapeutic benefit to affected tissues and organs throughout the body. In addition, we believe that our personalized busulfan conditioning regimen has the potential to allow the therapeutic benefits of our gene therapies to cross the blood-brain barrier and treat symptoms arising in the central nervous system. These often severe symptoms are typically unaddressed by the current standards-of-care for lysosomal disorders.
- *Broad patient applicability.* HSC gene therapies have been used to deliver treatments to patients of all ages, including children, and to patients who may be ineligible for other types of gene therapy due to the presence of

preexisting antibodies that detect viral vectors and trigger the immune system to destroy the vector and cells infected by the vector.

- *Restoration of protein function.* By contrast to the standard-of-care enzyme replacement therapy, which seeks to clear toxic substrate as a key symptom of a non-functioning gene, restoration of gene function may deliver a wide array of additional biochemical benefits throughout the body.
- *Tolerability in clinical trials.* To date, we have not seen any unexpected safety events in 24 patients across four clinical trials, with the longest follow-up more than 5 years to date.
- *Larger and varied payloads.* In contrast to other viral vectors, lentiviral vectors have the capacity to carry larger gene sequences, which allow them to potentially address a large variety of indications.

Strategic Selection of Our Initial Indications

There are approximately 70 identified lysosomal disorders, which are characterized by an abnormal toxic build-up of substrates and their metabolites in the body's cells. We are currently targeting Gaucher disease (type 1 and type 3), cystinosis, Hunter syndrome and Pompe disease. Each of these disorders affects a meaningful number of patients, has a suboptimal standard of care with unmet medical need and, we believe, is appropriate for HSC gene therapy. We believe our approach has the potential to address the shortcomings of existing therapies that, despite chronic dosing, cannot halt or reverse disease progression, restore normal lifespan or adequately address symptoms arising in both the peripheral tissues and the central nervous system.

Expanding the Utility of HSC Gene Therapy with Optimized Conditioning Regimens

A core part of our approach is to expand the use of HSC gene therapy to treat numerous lysosomal disorders. We believe conditioning is an essential step to optimize these treatments as it is designed to clear space in the patient's bone marrow and central nervous system for cells carrying the therapeutic gene. This maximizes the potential for their long-term engraftment which may enhance durability of therapeutic effect. We believe enabling patient and physician choice of conditioning agents has the potential to be a substantial advance in the gene therapy field, and are evaluating the implementation of a tailored conditioning approach for certain disease indications.

We plan to continue using busulfan conditioning and intend to strive to optimize its tolerability profile. We have pioneered precision dosing of busulfan in gene therapy in a single treatment cycle, with the goal of enhancing the patient experience. A body of research has identified an optimal exposure range for busulfan (Bu-90). Our approach is to personalize conditioning to each patient using TCI, a precision dosing program. TCI is designed to allow for continually controlled exposure by assessing via simple blood draws how rapidly the individual patient metabolizes busulfan, to inform further administration. Use of busulfan in a conditioning regimen causes side effects and can transiently compromise the patient's immune system, known as neutropenia, and reduce blood clotting, known as thrombocytopenia. The higher the level of conditioning, the greater the potential risk of more serious complications, such as veno-occlusive disease. However, we believe our approach to conditioning has the potential for reduced, predictable and manageable short- and long-term toxicities and maximized long-term engraftment.

In addition to our utilization of busulfan, we are exploring the implementation of monoclonal antibody conditioning as a potential alternative conditioning approach for certain indications and have entered into a collaboration agreement with Jasper Therapeutics.

plato®: Our Commercial-Scale Platform

In addition to developing first-line gene therapies, an important key to our strategy is to continuously improve our technology and production processes and to leverage these improvements across our gene therapies, if approved. plato is designed to provide the foundation for the potential worldwide commercialization of our gene therapies. It is a HSC gene therapy platform incorporating multiple upgrades including a four-plasmid lentiviral vector designed to optimize vector copy number, transduction efficiency and resulting enzyme activity; a closed, automated manufacturing system designed to improve consistency and predictability of the drug product; and a personalized approach to conditioning. plato has been used to dose a total of 10 patients in our clinical trials, which includes six patients from our FAB-GT trial for which enrollment was halted, and four patients from our Guard1 trial for Gaucher disease type 1. We intend to utilize the plato platform for all future patients enrolling in our Company-sponsored clinical trials. We believe our plato platform may lead to better patient outcomes and will represent a significant advance in our industry towards achieving the quality and scale required for global commercialization of gene therapies.

Our plato platform is designed to feature:

- *Large scale vector production:* We currently have manufacturing capabilities, through contract manufacturing organizations, or CMOs, at 200-liter bioreactor scale, with vector production capable of treating a substantial number of patients per year.
- *Global reach*: Our automated, closed system for manufacturing is designed to allow for the flexible production of our gene therapies. The automated, closed manufacturing system is portable with proprietary AVROBIO algorithms which allow for efficient establishment of manufacturing capabilities in multiple geographies that can be expanded or adjusted as our global supply requirements evolve. We believe this planned approach will facilitate global manufacturing and shipping of our gene therapies, and will promote access to our products by patients and caregivers.
- *Quality of manufacturing*: Our platform is designed to utilize current good manufacturing practices, or cGMP, and we believe our automated, closed manufacturing system may result in less production variability and reduce the risk of operator error, while enhancing the potency of the drug product. We believe these features will improve the quality of our gene therapies that are produced.
- *Patient convenience*: Our gene therapies are cryopreserved, which is a feature designed to promote a longer shelf-life. We believe that a longer shelf-life will allow patients and clinics to schedule treatment sessions with greater convenience.
- *Cost containment*: Our platform is designed to control fixed and variable expenses associated with manufacturing our gene therapies.

We believe the plato platform will form the backbone of our future commercialization efforts and our goal to take gene therapy mainstream.

Next Generation Vector Technology

We have utilized our core expertise in the development and optimization of lentiviral vectors to improve the vectors used in our gene therapies. We have made and expect to continue to make enhancements to our lentiviral vectors to improve safety, efficacy and efficiency. For example, clinical trials of AVR-RD-01 first utilized our original academic three-plasmid-produced lentiviral vector, which we refer to as LV1. However, we dosed six patients in our now halted FAB-GT clinical trial of AVR-RD-01 and the first four patients in our ongoing Guard1 clinical trial of AVR-RD-02 using our proprietary four-plasmid lentiviral vector, which we refer to as LV2, and expect to dose all future patients in our Company-sponsored trials with LV2. Our goal is to employ vectors that are state-of-the-art and that can be produced in a cost-effective and scalable manner.

Automated, Closed Manufacturing System

Our team has significant experience in cell processing and commercial-scale cellular therapy manufacturing. We have developed and are implementing a detailed plan for more cost efficient and scalable manufacturing of our gene therapies. In contrast to a number of other gene therapy companies that have not developed their commercial scale plans from the outset, we have executed on our plans to move to a closed suspension bioreactor system for vector production, as well as a closed, automated system for manufacturing our gene therapy product. Our move to a closed, automated manufacturing system was completed in 2019 as part of implementing upgrades from our plato platform, and six patients in our now halted FAB-GT clinical trial of AVR-RD-01 and the first four patients in our ongoing Guard1 clinical trial of AVR-RD-02 were each dosed using this system.

Our manufacturing approach is intended to allow for the production of drug product using relatively small, self-contained devices, which may reduce our reliance on large traditional clean rooms that are expensive to establish and maintain. We believe our manufacturing approach may result in greater flexibility in the location of manufacture and help to control costs associated with traditional manufacturing. In addition, we believe our automated manufacturing process may reduce operator error and yield greater consistency and less variability in the manufactured drug product.

We currently plan to rely on one CMO site, located in the United States, as a sole source provider of drug product for our Company-sponsored clinical trials worldwide.

Optimization of Conditioning Regimen

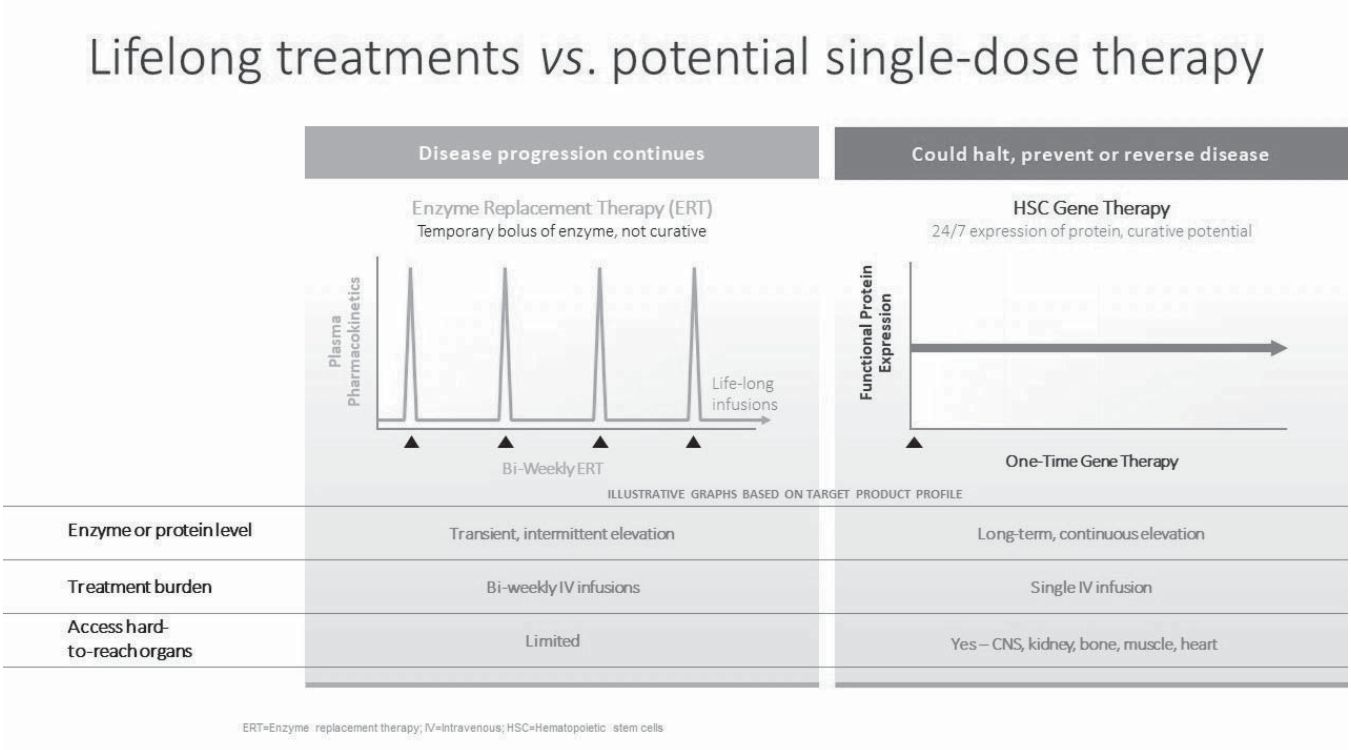
The conditioning regimen that we first employed utilized melphalan, a common chemotherapy drug, to ablate the patient's bone marrow. As part of the upgrades to our plato platform, we transitioned to utilizing busulfan, another chemotherapy drug, that has been in use since the 1950's. Busulfan is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic stem cell transplantation for chronic myeloid leukemia. Busulfan is routinely used in conditioning regimens before allogeneic stem cell transplantations for both malignant and non-malignant conditions. It has also been used as a single-agent, or in combination with an immunosuppressive agent, such as cyclophosphamide, in conditioning regimens prior to *ex vivo* gene therapy transplants.

Busulfan permits utilization of TCI in our conditioning regimen, thereby enabling physicians to personalize the dosing to each patient by titrating over four days to potentially enhance patient tolerability to the conditioning procedure and promote cell engraftment. By contrast, melphalan is administered once with no TCI, and may cause concerns regarding conditioning-related toxicity across patients due to individual differences in metabolism of the drug. In addition, we believe that the utilization of busulfan in our conditioning regimen has the potential to allow our gene therapies to cross the blood-brain barrier, a feature which may yield therapeutic benefit in diseases that have a central nervous system component, such as Gaucher disease type 3, Hunter syndrome, Pompe disease and other rare and non-rare diseases.

Advantages of Our Approach over Existing Therapies

We believe our gene therapy candidates offer several potential advantages over existing therapies for lysosomal disorders, including:

- *Curative impact that has the potential to halt or reverse disease progression.* Existing ERTs for Gaucher disease, Hunter syndrome and Pompe disease, and oral therapies for cystinosis, provide some therapeutic benefit to patients. However, because of their suboptimal pharmacokinetics, these ERTs only transiently increase plasma enzyme levels and the therapies for cystinosis require multiple doses throughout the day. In contrast, our lentiviral-based gene therapies are designed to enable the body to constantly produce the functional enzyme or other protein. This can potentially halt pathological damage and, depending on the targeted indication and organ system, may even reverse disease progression. Our investigational HSC gene therapies may provide potentially curative treatment to patients. This concept is illustrated in the graphs below.



- *Durable, single-dose treatment.* Our gene therapies offer the potential for a single dose to replace life-long, bi-weekly infusions or daily oral therapies that are often accompanied by numerous side effects and impact patients' quality of life. Our gene therapies are designed to transform the patient's own cells into a drug product that enables the continuous delivery of functional enzyme or other protein throughout the body after a single dose.
- *Reduced treatment cost over a patient's lifetime.* Existing ERTs and oral therapies can cost millions of dollars over a patient's lifetime because these therapies require frequent doses of expensive treatments to manage symptoms. Our single-dose gene therapies are designed to replace the costly chronic intravenous and oral therapies that are the current standard of care for patients with lysosomal disorders.

AVR-RD-02, Our Gene Therapy for Gaucher Disease (Type 1 and Type 3)

We are developing AVR-RD-02 for the treatment of Gaucher disease type 1 and type 3). We plan to manufacture AVR-RD-02 from hematopoietic stem cells that are first harvested from the patient, modified to add the gene that encodes for glucocerebrosidase, or GCase, and then infused into the patient.

Patient enrollment has commenced and is ongoing for the Phase 1/2 Guard1 clinical trial of AVR-RD-02 in patients with Gaucher disease type 1, and as of March 1, 2023 we have dosed four patients. The Guard1 trial is actively recruiting additional potential patients for our currently active sites.

We are planning for a Phase 2/3 clinical trial of AVR-RD-02 in pediatric and young adult patients with Gaucher disease type 3, which we refer to as the Guard3 clinical trial. We expect to open our first clinical trial site in the United Kingdom or the United States in the second half of 2023, subject to regulatory clearance by the MHRA or the FDA, as applicable. Initiation of additional clinical trial sites in Europe is expected at later dates and will be subject to regulatory clearance by the EMA and the relevant national regulatory authorities, as applicable.

Disease Overview

Gaucher Disease Type 1

Gaucher disease type 1 is the non-neuronopathic form of Gaucher disease, a rare, autosomal recessive, lysosomal disorder caused by a hereditary deficiency of functional GCase, an enzyme responsible for degrading glucocerebroside, a cell membrane building block, into glucose and lipids within lysosomes of cells. In patients with Gaucher disease type 1, the recycling of glucocerebroside from the breakdown of old red and white blood cells is inhibited, leading to its accumulation in macrophages. These abnormal macrophages, known as Gaucher cells, accumulate in multiple organs, particularly the liver, spleen and bone marrow.

Gaucher disease type 1 is one of the most common lysosomal disorders. It is diagnosed in approximately one in 44,000 births worldwide and is more prevalent in certain ethnic groups, such as people of Ashkenazi Jewish heritage. Approximately 90% of patients suffering from Gaucher disease in western countries have Gaucher disease type 1, which manifests as multiple morbidities including enlargement of the spleen and liver, low red blood cells, or anemia, low platelet count, or thrombocytopenia, and bone abnormalities including bone pain, fractures and arthritis. Bruising, risk of bleeding and fatigue are common due to the thrombocytopenia and anemia. Compared with the general population, patients with Gaucher disease type 1 have an approximately 20-fold increased risk of developing Parkinson's disease. Gaucher disease type 1 does not have manifestations of central nervous system symptoms.

Gaucher Disease Type 3

Gaucher disease type 3 is the subacute, chronic neurological form of Gaucher disease, a rare, autosomal recessive, lysosomal disorder caused by a hereditary deficiency of functional GCase, an enzyme responsible for degrading glucocerebroside, a cell membrane building block, into glucose and lipids within lysosomes of cells. In patients with Gaucher type 3 disease, the recycling of glucocerebroside from the breakdown of old red and white blood cells is inhibited, leading to its accumulation in macrophages. These abnormal macrophages, known as Gaucher cells, accumulate in multiple organs, particularly the liver, spleen and bone marrow. In addition, glucosylceramide accumulates in perivascular macrophages and brain glial cells and neurons leading to neuronal death. Clinically, central nervous system manifestations of Gaucher disease type 3 appear in childhood or adolescence, typically within the latter part of the first decade for the majority of patients, although the course of disease is markedly heterogenous.

Gaucher disease type 3 is estimated to occur in one in 100,000-300,00 births and is more prevalent in certain ethnic groups, such as people of Swedish Norrbottnian descent. Systemic manifestations of Gaucher disease type 3 may include enlargement of the spleen and liver, low red blood cells, or anemia, low platelet count, or thrombocytopenia, and bone abnormalities including bone pain, fractures and arthritis. Bruising, risk of bleeding and fatigue are common due to the thrombocytopenia and anemia. Variable other features of Gaucher disease type 3 include pulmonary infiltrates and esophageal varices associated with liver cirrhosis. Presentation of diverse neurologic features may begin at any time during infancy and early childhood with the most prevalent finding of horizontal supranuclear gaze palsy. Other manifestations of neurological disease include generalized seizures, myoclonus, ataxia, and/or dementia.

Limitations of Current Therapies

Gaucher disease type 1 is currently treated with bi-weekly infusions of ERT consisting of recombinant GCase over a patient's lifetime. The most commonly prescribed ERTs for Gaucher disease are Cerezyme, marketed by Sanofi, and VPRIV, marketed by Takeda. Pfizer markets ELELYSO, an ERT indicated for Gaucher disease type 1.

Although long-term ERT for Gaucher disease type 1 results in some therapeutic benefit, ERTs leave patients with significant unmet needs. Twenty-five percent of patients with Gaucher disease continue to experience physical limitations following two years of ERT, and a clinically significant percentage of patients continue to experience bone pain, thrombocytopenia and enlargement of spleen following ten years of ERT. In a published study of ERT therapy for Gaucher disease type 1, six target goals were evaluated, including parameters for hemoglobin and platelet levels, spleen and liver volumes, and general bone pain and severe disabling bone pain known as bone crisis. Following at least four years of ERT in this study, approximately 60% of patients failed to achieve one or more of these six target goals.

In addition to ERTs, the FDA has approved several oral therapies for the treatment of Gaucher disease, including Zavesca (miglustat) marketed by Actelion and Cerdelga (eliglustat) marketed by Sanofi. We believe these oral therapies also provide suboptimal treatment. Zavesca is approved as a second line therapy and is associated with significant toxicities, including diarrhea, weight loss and tremors. Cerdelga is not approved for use in children, has highly variable metabolism due to patient-to-patient genetic variations and is highly susceptible to interactions with other drugs.

Both ERTs and oral therapies for Gaucher type 1 impose significant costs on the healthcare system. We estimate that the average five-year cost to the healthcare system per Gaucher patient (all types) prescribed standard of care treatment in the United States is approximately $2.3 million. In 2022, Sanofi's Cerezyme and Cerdelga together generated worldwide net sales of approximately €995 million euros and Takeda's VPRIV generated worldwide net sales of approximately 47 billion Japanese yen.

Current therapies used to treat Gaucher disease type 1, namely, ERT and SRT, do not penetrate the brain and therefore have no effect on the neurological aspects of Gaucher disease type 3. The most commonly prescribed ERTs for Gaucher disease are Cerezyme, marketed by Sanofi, and VPRIV, marketed by Takeda.

Patients with Gaucher disease type 3 may exhibit wide variation of disease progression with the severity of systemic disease and neurological deficits differing considerably between patients. In a published study of SRT therapy for Gaucher disease type 3, no significant benefits were demonstrated on the neurological manifestations of Gaucher disease type 3. Although long-term ERT for Gaucher disease type 3 results in some therapeutic benefit on visceral, hematological and bone manifestations, ERTs leave patients with significant unmet needs owing to persisting accumulation of substrate within the central nervous system. Following 10 years of ERT, two patients' epilepsy had worsened while a third patient developed epilepsy around eight years after treatment initiation. Another published study on ERT showed that enzyme infusions had no effect on patients with myoclonus and approximately 40% of patients deteriorated neurologically during a median 3.5 year follow-up period.

Our Solution

We are developing AVR-RD-02 to potentially provide a functional cure to patients with Gaucher disease type 1 and type 3 with a single dose of the patient's own hematopoietic stem cells modified in an *ex vivo* procedure. AVR-RD-02 is a HSC gene therapy that contains a codon-optimized human gene and is designed to maximize the likelihood of sustained GCase production in hematopoietic stem cells and their progeny.

Ongoing Phase 1/2 Clinical Trial (Guard1)

We have initiated our Guard1 Phase 1/2 clinical trial of AVR-RD-02 in patients with Gaucher disease type 1. Patient enrollment has commenced, and as of March 1, 2023, four patients have been dosed. This clinical trial is actively recruiting additional potential patients for our currently active sites. Our initial clinical trial is open to treatment-naïve patients; patients who have been stable on ERT for at least 24 months; and patients who have not received ERT or substrate reduction therapy, or SRT, in the past 12 months. We intend to enroll 8 to 16 patients, between the ages of 18 and 50, with Gaucher disease type 1. Patients currently prescribed ERT will cease treatment for the duration of the clinical trial. All enrolled patients will receive a single treatment with AVR-RD-02 and will be followed for 52 weeks to measure safety and efficacy. We intend to utilize our plato platform for all patients enrolling in our Phase 1/2 clinical trial of AVR-RD-02. Our efficacy endpoints for this clinical trial will include visceral domain and hematologic measures such as liver and spleen volumes, hemoglobin, platelet counts, bone pain and bone density measures, and quality of life measures along with critical biological blood markers used to track the disease progression in Gaucher disease type 1.

In December 2022, we presented data on the first four patients in the Guard1 clinical trial, which is described below.

Vector Copy Number (VCN)

All four adult GD1 patients in the Guard1 clinical trial who have been infused with investigational AVR-RD-02, based on data as of November 2022, achieved a VCN between 0.54 to 0.86 per diploid genome, 14 weeks to two years post gene therapy. We believe this indicates sustained engraftment and the presence of the transgene in the peripheral blood leukocytes, the essential cell impacted in Gaucher disease patients.

Plasma Lyso-Gb1 Reductions

Glucosylsphingosine, or lyso-Gb1, is considered a surrogate marker for disease activity and treatment response for Gaucher disease type 1. In the case of ERT-naïve patients and patients who have discontinued ERT, we believe that reductions in lyso-Gb1 levels following treatment with gene therapy are likely driven by the therapeutic effect of gene therapy. In all four adult Gaucher disease type 1 patients dosed to date in the Guard1 clinical trial, based on data as of November 2022, we observed that lyso-Gb1 decreased 21% to 70% (21%, 21%, 30% and 70%, respectively) below ERT baseline levels for all four patients, 12 weeks to two years post gene therapy. In this study baseline ERT is the measurement of single plasma lyso-Gbl value observed prior to initiating mobilization. Lyso-Gbl is a downstream metabolic product of glucocerebroside and is considered a sensitive and specific biomarker used for disease monitoring in patients with Gaucher disease.

Plasma Chitotriosidase Reductions

Chitotriosidase is a biomarker of macrophage activation that is found in high levels in Gaucher disease patients where the macrophages have accumulated an excess lipid burden. In the Guard1 clinical study, the metabolite chitotriosidase was reduced in the two patients with evaluable samples, reflecting a reduction in macrophage activation and inflammation. Patient 1's chitotriosidase level has declined from a high of 145.8 μmol/L/h prior to gene therapy treatment to 42.4 μmol/L/h (≤38.1 μmol/L/h is considered normal range) two years post gene therapy. Patient 2, who was in the normal range before gene therapy treatment, still decreased from 24.3 μmol/L/h at baseline to 19.2 μmol/L/h at week 52. Samples from the other two adult patients dosed to date are not evaluable.

In this study, baseline ERT is the measurement of a single chitotriosidase value observed prior to initiating mobilization.

Liver and Spleen Volume Reductions

In three of the four adult patients dosed with AVR-RD-02, as of November 2022, a demonstrated reduction in liver and spleen volumes below the ERT baseline was observed. Patient 4 was not yet scanned as of the data cutoff date for liver or spleen volume. In the patients who were scanned, we observed the following results.

- Patient 1 data showed a clinically significant 24% reduction in liver volume at 104 weeks post gene therapy (patient underwent a splenectomy during childhood).
- Patient 2 data showed a clinically significant 11% reduction in liver volume and 23% reduction in spleen volume at 52 weeks post gene therapy.
- Patient 3 data showed a 4% reduction in liver volume and a 19% reduction in spleen volume, at 26 weeks post gene therapy.

Hemoglobin Concentration and Platelet Counts

Gaucher disease type 1 typically causes patients to have low levels of hemoglobin and platelets. In this study, the baseline measurement was taken one month prior to discontinuation of ERT. Twelve weeks to two years post gene therapy, hemoglobin and platelet levels, as of November 2022, were in normal range following gene therapy for all four adult patients in the Guard1 clinical trial.

Safety Data

As of the most recent cut-off date of September 27, 2022, safety data from the four adult patients dosed indicated no AEs related to drug product. All AEs observed were related to myeloablative conditioning, stem cell mobilization, underlying disease or pre-existing conditions. The majority of AEs were mild or moderate and resolved without clinical sequelae. As of the safety cut-off date of September 27, 2022, all AEs had resolved except for one AE of amenorrhea, which remains unresolved and ongoing.

Because this clinical trial is ongoing, safety and efficacy data are preliminary and subject to change. As is typical in open-label studies in which interim reports are provided, the data are regularly reviewed and validated. As a result, certain data may change over time, including reductions or increases in the number of reported safety events as well as the characterization of the severity or relatedness of safety events, until the database is locked at the end of the study.

Data From First Pediatric Gaucher Disease Type 3 Patient Dosed with AVR-RD-02

In December 2022, we announced that an 11-year-old patient with Gaucher disease type 3 was dosed with AVR-RD-02 at the University of Manchester, U.K., on a named patient basis, and we presented the named patient data at our virtual Gaucher disease Program Update. The patient's physicians then presented additional data at the WORLD*Symposium* in February 2023.

At 581 days post gene therapy, the patient has normalized peripheral blood leukocyte glucocerebrosidase, or GCase, enzyme activity and plasma chitotriosidase, a marker of activated macrophages, and remains off ERT and SRT. The patient's albumin levels increased 15 to 21 g/L at 1.2 years post gene therapy, reflecting improvements in lymphadenopathy and enteropathy. This patient was previously refractory to maximal and multimodal medical therapy, including ERT, SRT, enteral steroids and dietary restrictions. Additionally, the patient did not develop any new lesions on MRI assessments post gene therapy and had no clinically detectable change in neurological status or new neurological manifestations 15 months post gene therapy.

To date, safety data from this patient indicate no adverse events, or AEs, related to drug product. All AEs observed were related to myeloablative conditioning, stem cell mobilization, underlying disease or pre-existing conditions.

Planned Clinical Trial of AVR-RD-02 for Gaucher Disease Type 3 (Guard3)

A Phase 2/3 Guard3 clinical trial of AVR-RD-02 in patients with Gaucher disease type 3 is currently planned, with initiation anticipated in the second half of 2023, subject to regulatory alignment. The Guard3 trial is anticipated to be a global, open label, parallel-arm and randomized controlled clinical trial to evaluate the efficacy and safety of AVR-RD-02 in pediatric and young adult patients. The Guard3 trial is expected to include approximately 40 Gaucher disease type 3 participants (male or female), randomized on a 1:1 basis to receive either AVR-RD-02 HSC gene therapy or continue to receive standard of care ERT. Currently, the Guard3 trial design anticipates that following the observation period, eligible participants who received ERT will be eligible to cross over into the active arm to receive AVR-RD-02 HSC gene therapy.

The planned primary efficacy endpoint is a novel, multi-domain endpoint to reflect the systemic and heterogeneous nature of Gaucher disease, including ataxia (impaired coordination), breathing ability and liver and spleen volume. A key secondary efficacy measure plans to examine substrate levels in cerebrospinal fluid, or CSF, which reflects the impact of the HSC gene therapy in the central nervous system, or CNS.

The design of the planned Phase 2/3 clinical trial of AVR-RD-02 in patients with Gaucher disease type 3 is still subject to regulatory agency review and clearance, and final trial design may differ from current plans, including changes based on regulatory agency feedback.

We intend to utilize our plato platform for all patients who enroll in our planned Phase 2/3 Guard3 clinical trial and receive HSC gene therapy.

Overall, data from both the Guard1 and planned Guard3 clinical trials are expected to leverage the similar underlying pathophysiology for both types of Gaucher disease.

AVR-RD-04, Our Gene Therapy for Cystinosis

Together with UCSD, we are developing CTNS-RD-04, which we refer to as AVR-RD-04, for the treatment of patients with cystinosis. AVR-RD-04 is manufactured from hematopoietic stem cells that are first harvested from the patient, modified to add the gene that encodes for cystinosin, and then infused into the patient. AVR-RD-04 is currently being studied by our collaborators at UCSD in a Phase 1/2 collaborator-sponsored clinical trial. As of March 1, 2023 six patients have been dosed with AVR-RD-04 and the trial is fully enrolled. In February 2023, our collaborators at UCSD reported updated interim data from the Phase 1/2 collaborator-sponsored clinical trial of AVR-RD-04 at the 2023 WORLD*Symposium* in Orlando, Florida. We expect to provide clinical and regulatory updates on the Phase 1/2 clinical trial of AVR-RD-04 at ASGCT in May 2023.

In September 2022, the FDA granted RPDD for AVR-RD-04 for the treatment of cystinosis. AVR-RD-04 has previously received Fast Track Designation from the FDA and ODD from the FDA and EMA.

In the first quarter of 2023, we completed a scientific advice meeting with MHRA and received feedback from the FDA regarding a planned Company-sponsored clinical trial for AVR-RD-04. Based on these regulatory interactions and feedback and subject to regulatory clearance, we are planning to initiate activities for a Company-sponsored Phase 1/2 clinical trial for cystinosis in the second half of 2023, which is designed to be registration-enabling. Clinical sites are anticipated in the United Kingdom, Europe and the United States. Our current plan involves a two-part clinical development strategy, including both a pre-renal transplant population clinical trial and a post-renal transplant population clinical trial.

Disease Overview

Cystinosis is a rare, genetic, autosomal recessive, lysosomal disorder caused by the accumulation of cystine, the oxidized dimer of the amino acid cysteine. Cystine is normally transported through the lysosomal membrane to the cytosol where it is reutilized after its transformation to cysteine. In cystinosis, cystine accumulates inside the lysosomes because of a defect in the gene that encodes cystinosin, the protein that transports cystine across the lysosomal membrane. Cystine is poorly soluble and forms crystals as its concentration increases. These crystals build up and cause complications in many organs and tissues. The kidneys and eyes are especially vulnerable to damage, and the muscles, thyroid, pancreas and testes may also be affected.

The most severe form of cystinosis begins in infancy, causing poor growth and a particular type of kidney damage in which certain molecules, such as glucose, amino acids, phosphate, and bicarbonate, that should be reabsorbed into the bloodstream are instead eliminated in the urine. These renal problems ultimately lead to impaired growth and may result in soft, bowed bones, especially in the legs. By the time the patient is approximately two years old, cystine crystals may be present in the cornea, and the buildup of these crystals in the eye causes pain and an increased sensitivity to light. Untreated children with cystinosis may experience complete kidney failure by the age of ten. Other signs and symptoms that may occur in untreated patients, especially after adolescence, include muscle deterioration, blindness, inability to swallow, type 1 diabetes mellitus, hypothyroidism, and central nervous system problems. More than 90% of untreated patients require a kidney transplant before the age of 20. It is estimated that cystinosis disease is diagnosed in approximately one in 170,000 people.

Limitations of Current Therapies

Cystinosis is currently treated with oral formulations of cysteamine that enter the lysosome and stimulate the breakdown of cystine into products that do not require the cystinosin protein to be transported. Oral treatment can delay the development of kidney failure by six to ten years if it is started at a very early age, however it cannot prevent kidney failure or the development of other complications, such as the formation of cystine crystals in the cornea. The most commonly prescribed oral therapies for cystinosis are Procysbi (delayed release cysteamine bitartrate), marketed by Horizon Orphan, and Cystagon (cysteamine bitartrate), marketed by Mylan and Recordati S.p.A. In 2021, Procysbi generated worldwide net sales of approximately $190 million. We estimate that the average five-year cost to the healthcare system per cystinosis patient prescribed standard of care treatment in the United States is approximately $4.3 million.

Procysbi and Cystagon must be taken orally every 12 or 6 hours, respectively, leading to significant pill burden and compliance challenges. Because cysteamine works by directly binding to cystine, rather than through a typical small molecule that inhibits an enzyme or receptor, a substantial quantity is required. For adults, this can mean taking at least 12 capsules twice a day, every day. Oral therapy with cysteamine is associated with a high degree of noncompliance due to the frequency with which it must be dosed and the accompanying nausea, as well as the acrid sulfur smell that it produces in the breath and body. It has been estimated that only one third of patients are able to adhere to the strict dosing schedule. Studies have shown that adherence diminishes over time in adolescents and adults despite disease impact. Further, oral cysteamine treatment has no effect on ocular cystine crystals deposits, thus requiring patients to be treated with topical cysteamine eye drops which must be applied each hour the patient is awake.

Our Solution

We are developing AVR-RD-04 to potentially provide a functional cure to patients with cystinosis with a single dose of the patient's own hematopoietic stem cells modified in an *ex vivo* procedure. AVR-RD-04 is a HSC gene therapy containing a human gene for cystinosin designed to maximize the likelihood of sustained cystinosin production in hematopoietic stem cells and their progeny.

Ongoing Phase 1/2 Collaborator-Sponsored Clinical Trial

In the ongoing collaborator-sponsored Phase 1/2 clinical trial of AVR-RD-04, six patients with cystinosis who have previously been treated with cysteamine have been dosed. This clinical trial is being conducted by UCSD and has been funded in part by grants to UCSD from the California Institute for Regenerative Medicine, Cystinosis Research Foundation and National Institutes of Health. The clinical trial's primary endpoints are safety and tolerability, assessed for up to two years after treatment. Secondary endpoints to assess preliminary efficacy include change from baseline in cystine levels in rectal mucosa and granulocytes, as well as cystine crystal counts in the cornea and skin. These secondary efficacy endpoints will also be evaluated through clinical tests of kidney function, ophthalmologic measures, muscle strength, pulmonary function and neurological and psychometric function, as well as through patient-reported outcomes and assessments of health-related quality of life. Mixed leukocyte and granulocyte cystine concentration measures have been part of cystinosis standard of care treatment for the past two decades, and changes in the average level of cystine in granulocytes from baseline was originally a primary endpoint of the clinical trial of AVR-RD-04. However, we and our collaborators at UCSD determined that cystine concentration in leukocytes and granulocytes, which is used to monitor small molecule therapies, is not appropriate to represent the mechanism of action of a gene therapy. As a result, the protocol for this clinical trial was amended in 2020 to retain safety and tolerability as the primary endpoint, as is appropriate for this stage of development, and shift measurement of cystine in granulocytes to a secondary endpoint.

Because this is a collaborator-sponsored clinical, the study drug is not manufactured using our plato platform, and neither the automated, closed manufacturing system nor LV2 is used in connection with this clinical trial.

As of February 2023, the first five patients in the trial had discontinued and remained off oral cysteamine, with the first patient out to 36 months post-treatment. Additionally, four of the five dosed patients had discontinued and remained off cysteamine eye drops as of May 6, 2022. The second patient in the trial, who had stopped cysteamine eye drops one-month post-treatment with AVR-RD-04 per the trial protocol, resumed cysteamine eye drops in July 2021.

Vector Copy Number

In February 2023, our collaborator presented interim VCN data for the first five patients dosed in the Phase 1/2 clinical trial ranging from 0.7 and 2.0 per diploid genome between three- to 27-months post gene therapy.

Cystine Crystals in Skin and Gastrointestinal Mucosa Biopsy Tissues

Skin and gastrointestinal mucosa biopsies have been performed on patients at baseline and post-treatment with AVR-RD-04. The data from the biopsies are intended to show the average skin intracytoplasmic crystals per cell, which is a measurement of the number of toxic crystals in each cell. In February 2023, our collaborator at UCSD reported biopsy data in skin and gastrointestinal mucosa. In the skin, reductions in average intracytoplasmic crystals per cell ranged from 8% in patient 1, 64% in patient 2 and 81% in patient 3 below the patients' own standard-of-care baseline measures at 12-27 months post gene therapy. In gastrointestinal mucosa, a measurable reduction below patients' own standard-of-care baseline measures was observed post gene therapy, including a 73% reduction after 27 months for patient 1, a 28% reduction after 12 months for patient 2, an 86% reduction after 12 months for patient 3, and a 21% reduction after 6 months for patient 4. These data suggest the systemic distribution of functional cystinosis protein is impacting a variety of measures throughout the body. As of February 2023, our collaborator at UCSD had not yet reported skin biopsy data for patients 4, 5 and 6 or gastrointestinal mucosa biopsy data for patients 5 and 6.

Levels of Cystine in Cornea

Levels of corneal cystine crystals are being assessed in this clinical trial using IVCM. In May 2022, we presented a set of images of the first patient's cornea measured at baseline and 18-months post-administration. The baseline IVCM images were taken using a Nidek ConfoScan microscope and the subsequent images were taken using a Heidelberg (HRT3) with Rostock Cornea Module microscope. Each of the post-treatment images showed a noticeable decline in the presence of corneal crystals. The images were preliminarily scored by a physician, on a scale of zero to four, to quantify crystal deposition in each corneal layer of the central cornea. In a patient-reported outcome scale of photophobia severity, the first three patients for which data are available, reported improved or stable photophobia scores. Patient 1, who entered the trial with a higher level of cystine crystal accumulation in the eye, reported a two-point photophobia score improvement 24 months post gene therapy. Patients 2 and 3, who both entered the trial with relatively lower cystine crystal accumulation in the eye, reported stable photophobia scores, both at 12 months post gene therapy. Patients 1, 3, 4 and 5 remain off cysteamine eye drops.

Kidney Function

Assessment of kidney function includes measurements of serum creatinine, or sCR, and eGFR, which is determined using the CKD-EPI formula. The first patient in the Phase 1/2 clinical trial exhibited an eGFR value of 18.1 mL/min/1.73m2 at 27 months post-treatment as compared to a baseline value of 55 mL/min/1.73m2. This patient's eGFR values had been trending downward in the three years prior to administration of AVR-RD-04. We expect this patient's eGFR levels to continue declining at a level consistent with the irreversible nature of nephropathic cystinosis. At six months post-treatment the second patient in the clinical trial, who received two kidney transplants prior to treatment in the clinical trial, exhibited an eGFR value of 81 mL/min/1.73m2 as compared to a baseline value of 71 mL/min/1.73m2.

Safety Data

As of the safety data cut-off date of January 9, 2023, preliminary interim clinical data for the first six patients dosed in the Phase 1/2 clinical trial appear to indicate that the AVR-RD-04 investigational gene therapy has been generally well tolerated with no unexpected safety events identified. There have been no reports of safety events attributed to the AVR-RD-04 drug product. As of the safety data cut-off date, a total of 173 adverse events, or AEs, were reported, a majority of which were reported by the investigator to be moderate or mild and resolved without clinical sequelae. All reported AEs were consistent with expectations for the underlying disease, stem cell mobilization and conditioning regimen prescribed by the study protocol.

The foregoing data on the Phase 1/2 clinical trial of AVR-RD-04 have been provided by our collaborators at UCSD and are subject to change. Additionally, because this clinical trial is ongoing, safety and efficacy data are preliminary and subject to change. As is typical in open-label studies in which interim reports are provided, the data are regularly reviewed and validated. As a result, certain data may change over time, including reductions or increases in the number of reported safety events, as well as the characterization of the severity or relatedness of safety events, until the database is locked at the end of the study.

AVR-RD-05, Our Gene Therapy for Hunter Syndrome

We are developing AVR-RD-05 for the treatment of mucopolysaccharidosis type II (MPSII), or Hunter syndrome. AVR-RD-05 involves *ex vivo* transduction of the patient's own hematopoietic stem cells with a therapeutic transgene, in-licensed from the University of Manchester, or UoM, designed to express functional iduronate 2-sulfatase, or IDS, which is the enzyme the patient needs to maintain cellular health, coupled to a proprietary ApoE2 protein tag that is designed to improve stability of the enzyme in the bloodstream and facilitate uptake by tissues.

AVR-RD-05 will be studied by our collaborators at UoM, and a Phase 1/2 collaborator-sponsored clinical trial of AVR-RD-05 is expected to be initiated in 2023.

Disease Overview

Hunter syndrome disease is a rare, recessive lysosomal disorder caused by a mutation in the gene that encodes for IDS that results in accumulation of the glycosaminoglycans heparan and dermatan sulfate. Hunter syndrome affects a multitude of organs and is a chronic and progressive multi-system disorder. Clinical manifestations in Hunter syndrome include skeletal abnormalities, known as dysostosis multiplex, short stature, joint stiffness, and hepatosplenomegaly, accompanied by cardiorespiratory symptoms. Severe cases of Hunter syndrome, which are most common, also feature progressive neurodegeneration, typically followed by death in teenage years due to obstructive airway disease and cardiac failure.

Hunter syndrome is an X-linked disorder, meaning the gene that is responsible is located on the X chromosome. Because males have only one X chromosome, an abnormal copy of the gene that causes Hunter syndrome is sufficient to cause the disease. The overall diagnosed incidence of Hunter syndrome is estimated to be approximately one in 100,000 to one in 170,000 males worldwide.

Limitations of Current Therapies

Hunter syndrome is currently treated with ERT delivered by weekly intravenous infusion. The onpreclinical dataly approved therapy for Hunter syndrome is Elaprase, marketed by Takeda, which generated worldwide net sales of approximately 80 billion Japanese yen in 2022. We estimate that the average five-year cost to the healthcare system per Hunter patient prescribed standard of care treatment in the United States is approximately $2.4 million.

Two-thirds of patients experience developmental and neurological decline, which is often noted by approximately age two. Due to lack of newborn screening, diagnosis usually occurs much later in patient's lives, around five years of age and can be as late as eight years. Although patients typically begin ERT treatment almost immediately after diagnosis, often the disease symptoms are far advanced and ERT is insufficient to halt the disease progression. ERT does not treat the neurological symptoms of the disease, and therefore a significant unmet need remains in a majority of patients with Hunter syndrome. Furthermore, anti-ERT antibodies are a limitation for a significant part of the patient population.

Our Solution

We, together with our collaborators at UoM, are developing AVR-RD-05 to potentially provide a functional cure to patients with Hunter syndrome. AVR-RD-05 is intended to be a gene therapy product containing a codon-optimized human gene for IDS attached to a ApoE2 protein tag designed to increase the cells' secretion of IDS to potentially restore healthy cellular function, stabilize the secreted IDS so it has a longer half-life, and facilitate uptake of IDS into the brain. In addition, we believe that the utilization of busulfan in our conditioning regimen may have the potential to allow AVR-RD-05 to cross the blood-brain barrier, a feature which may yield therapeutic benefit.

Preclinical Data

In November 2020, we presented previously published preclinical data on AVR-RD-05. The study presented data from normal study mice, mice affected with the equivalent of Hunter syndrome, mice treated with AVR-RD-05 modified to not incorporate the ApoE2 protein tag, and mice treated with AVR-RD-05 incorporating the proprietary ApoE2 tag. These data demonstrated the effect of AVR-RD-05 on levels and composition of heparan sulfate in the brain, neuro-inflammatory pathologies, facial and skeletal abnormalities, as well as cognitive performance and sensorimotor coordination and balance. We believe these data support the potential of AVR-RD-05 to treat this progressive disease, and potentially prevent the onset of severe symptoms if treated early.

Planned Phase 1/2 Collaborator-Sponsored Clinical Trial

Our collaborators at UoM plan to initiate a Phase 1/2 clinical trial in 2023. The Phase 1/2 clinical trial is expected to enroll five male patients, age three months to 12 months, with an early progressive form of the disease. The clinical trial is expected to be open to treatment-naïve patients as well as patients currently on ERT. The clinical trial's primary endpoints are expected to be safety and tolerability. Secondary endpoints to assess preliminary efficacy are expected to include measurements of peripheral expression of IDS activity in plasma, CSF, and leukocytes; heparin sulfate concentration in CSF, plasma and urine; VCN per diploid genome, proportion of cells containing the inserted gene in total bone marrow colony forming units; cognitive function; and various behavioral and quality of life measurements.

Because this is a collaborator-sponsored clinical, the study drug will not be manufactured using our plato platform, and neither the automated, closed manufacturing system nor LV2 will be used in connection with this clinical trial.

AVR-RD-03, Our Gene Therapy for Pompe Disease

We are developing AVR-RD-03 for the treatment of Pompe disease. We will manufacture AVR-RD-03 from hematopoietic stem cells that are first harvested from the patient, modified to add the gene that encodes for acid alpha glucosidase A, or GAA, attached to a peptide sequence known as a glycosylation-independent lysosomal targeting, or GILT, tag and then infused into the patient. AVR-RD-03 will incorporate a GILT tag because the GILT tag has been found to increase the uptake of GAA into cells, especially in muscle cells by a multiple of 25, which is a particularly important target tissue for patients with Pompe disease and a target tissue that is considered difficult to access for ERT. AVR-RD-03 is designed to incorporate a potent promoter to increase volume of system enzyme in circulation.

Disease Overview

Pompe disease is a rare, autosomal recessive lysosomal disorder caused by a mutation in the gene that encodes for GAA that results in the buildup of glycogen, a complex sugar, in the body's cells. The accumulation of glycogen in certain organs and tissues, especially muscles, impairs normal tissue and organ function. Patients with Pompe disease experience serious muscle related problems, including progressive muscle weakness, especially in the legs and trunk, and the muscles that control breathing. As the disorder progresses, breathing problems can lead to respiratory failure.

The overall diagnosed incidence of Pompe disease is estimated to be approximately one in 58,000 people although frequency and disease progression varies with age of onset, ethnicity and geography. Overall diagnosed incidence of Pompe disease is projected to increase to one in 22,000 people as it is increasingly included in newborn screening panels.

The severity of Pompe disease symptoms and rate of progression is highly variable and correlated with age of symptom onset and the degree of enzyme deficiency. Infantile or early onset disease, the most severe form of Pompe disease, accounts for approximately 25% of all affected patients. Those with early-onset disease are usually diagnosed in the first few months of life and is associated with cardiomyopathy. Left untreated, these patients can die due to heart failure, respiratory distress or malnutrition resulting from feeding difficulties within the first year of life. Patients with late-onset disease typically have higher enzyme levels and usually have symptoms such as reduced mobility and respiratory problems but are not at increased risk of developing cardiomyopathy. Late-onset patients experience progressive difficulty walking and respiratory decline. While life expectancy can vary, Pompe disease is a life-limiting disease that can result in death due to complications from respiratory failure.

Limitations of Current Therapies

Pompe disease is currently treated with ERT delivered by bi-weekly intravenous infusion. Approved therapies for Pompe disease include Lumizyme (known as Myozyme outside of the United States), indicated for both infantile onset Pompe disease, or IOPD, and late onset Pompe disease, or LOPD. In addition, Nexviazyme (known as Nexviadyme outside of the United States) has been approved as an ERT for LOPD only. The products are marketed by Sanofi, which generated collective worldwide net sales of approximately €1.2 billion euros in 2022. We estimate that the average five-year cost to the healthcare system per Pompe patient prescribed standard of care treatment in the United States is approximately $3.2 million.

Though patients treated with ERT for Pompe disease have improved survival and respiratory function, ERT is not curative, and patients in long-term observational studies continue to have increased risk of respiratory failure and have residual muscle weakness including difficulties swallowing with risk of aspiration. One challenge with ERT treatment for Pompe disease is that a standard dose requires approximately twenty-fold more enzyme compared to standard doses for Fabry or Gaucher diseases. Large doses of Lumizyme that are delivered systemically in order to achieve potentially therapeutic levels in the target tissues result in approximately 90% of patients developing antibodies against the therapy. These antibody responses may impact both the efficacy and safety of Lumizyme. The FDA approval of Lumizyme and Nexviazyme carry black box warnings related to the risk of severe allergic and immune mediated reactions, including life-threatening anaphylaxis.

Our Solution

We are developing AVR-RD-03 to be a gene therapy product containing a codon-optimized human gene for GAA attached to a GILT tag designed to increase uptake of GAA in muscle cells. AVR-RD-03 will target patients with late onset Pompe disease, which represent the majority of patients with this disease. In addition, we believe that the utilization of busulfan in our conditioning regimen may have the potential to allow AVR-RD-03 to cross the blood-brain barrier, a feature which may yield therapeutic benefit. While we are continuing to advance AVR-RD-03, we are prioritizing our Gaucher disease and cystinosis clinical programs. As a result, we no longer expect to initiate a clinical trial for AVR-RD-03 in 2023.

Preclinical Data

In November 2020, we presented data from a study in which mice with the equivalent of classic infantile-onset Pompe disease were treated with AVR-RD-03. We believe these data support the potential of lentiviral-based gene expression of GAA to prevent some of the symptoms of GAA deficiency. These results also demonstrated the need to further increase the uptake of GAA into muscle cells to treat patients, which is a known challenge for ERTs and leads to the use of large quantities of enzyme to attempt to deliver effective treatment levels.

We believe we can use a GILT tag to address the known challenges of skeletal muscle uptake in patients with Pompe disease. Attachment of a GILT tag to a particular protein can increase the effective uptake of that protein into target tissues. We are designing AVR-RD-03 to use a GILT tag to facilitate GAA uptake into cells and thereby reduce the therapeutically required amount of GAA produced by a patient's cells following gene therapy treatment.

In mouse models of Pompe, administration of recombinant GAA with the GILT tag demonstrated significant reduction in glycogen in cardiac and skeletal muscles as compared to the administration of recombinant GAA alone. We licensed GILT tag technology from BioMarin Pharmaceutical Inc., or BioMarin, and are incorporating a GILT tag into our lentiviral vector with the goal of the patient producing GILT-tagged GAA following treatment with AVR-RD-03.

GAA Enzyme Production

Our preclinical study measured the levels of GAA observed in normal mice, mice with the equivalent of infantile-onset Pompe disease, mice treated with AVR-RD-03 modified to not incorporate our proprietary GILT tag, and mice treated with AVR-RD-03 including our GILT tag, in each case measured 16 weeks post-treatment. These data showed significant overexpression of GAA in bone marrow, white blood cells and plasma in mice treated with AVR-RD-03 without our GILT tag as well as AVR-RD-03 incorporating our GILT tag.

Glycogen Reduction

Our preclinical study also measured glycogen levels in the heart and brain at four months post-treatment with our GILT-tagged version of AVR-RD-03, which showed a 99% and 100% reduction, respectively, in glycogen levels. In addition, our study measured glycogen levels in various organs of the study mice at eight months post-treatment. The data showed an average of greater than 99% reduction in glycogen levels in the heart, greater than 97% reduction in the diaphragm, greater than 85% reduction in skeletal muscle, greater than 95% reduction in the brain, and greater than 99% reduction in the spinal cord.

Manufacturing

Industrializing Our Gene Therapies Through Our Outsourced Manufacture and Supply Network

We have established manufacturing relationships that we believe will provide us with drug product manufacturing capabilities to support all aspects of the development and eventual commercialization of our gene therapies. Our team has leveraged their broad expertise in the manufacturing of gene and cellular therapies to build a network of CMO partners for the development and manufacture of drug products and outsourced suppliers for the supply of vectors and plasmids. We currently rely, and expect to continue to rely, on sole source suppliers for vector supply, plasmid supply and cell culture media. In addition, although we have historically relied on multiple CMO partners for drug product manufacturing, we currently plan to use a sole source CMO as the provider of drug product for our ongoing and future Company-sponsored clinical trials. However, we believe that our third-party CMO partner and suppliers have capacity to accommodate current and future clinical trials and we are continuing to build a network that we expect will have capacity to generate sufficient quantities to meet our expected commercial needs.

To optimize production of our gene therapies, we have moved our cell processing to an automated, closed system using disposable supplies. We believe this industrialized manufacturing process will enable a repeatable approach through which we can design and manufacture commercially viable HSC gene therapies to potentially treat a large variety of genetic disorders. We expect that our automation of the manufacturing processes will further increase our CMO partners' manufacturing capacity.

Producing a Patient's Gene Therapy

We start the process to produce a patient's gene therapy with the mobilization of a patient's stem cells from the bone marrow to the blood stream and collect them via apheresis, a standard procedure used in stem cell transplants. The apheresis material is then transported to the manufacturing facility where we isolate the stem cells and treat these cells with a lentiviral vector to insert the equivalent of a functional copy of the gene that is mutated in the target disease. The manufacturing process typically takes approximately three days to complete. We preserve patients' modified cells at a very low temperature, using cryopreservation to maintain the cellular material in optimal condition until it is thawed prior to being infused into the patient. Cryopreservation of the product allows for long-term storage and the ability to conduct a number of quality control tests to validate the modified cells prior to introducing them into the patient. We believe cryopreservation will also enable us to supply our products globally, as well as significantly increase the convenience of infusion scheduling for clinicians and patients, compared to fresh *ex vivo* gene therapy products that may have shelf-lives of only 24 hours.

Prior to infusion of the gene therapy-modified cells into the patient, the patients undergo a conditioning regimen to remove some of the patient's unmodified cells from the bone marrow to create sufficient space for the modified hematopoietic stem cells to engraft and produce their progeny.

After the conditioning regimen is complete, the HSC-modified stem cells are infused into the patient by intravenous administration. After infusion, these cells are expected to engraft into the bone marrow, replicate and differentiate into all the various types of blood cells that will distribute throughout the body. These widely distributed cells potentially lead to sustained expression of the desired therapeutic enzyme or protein. The sustained expression of the functional enzyme or protein is a direct substitute for the protein currently delivered by ERTs, which require periodic infusions.

Intellectual Property and Other Barriers to Entry

The proprietary nature of, or protection for, our gene therapy technology, our product candidates, our production methods and supply chain are an important part of our strategy to develop and commercialize novel therapies. To maximize the commercial opportunity for our gene therapies, if approved, we and our partners have been building and continue to build barriers to entry by our competitors, including:

- We in-license and develop know-how, including data, relating to certain of our product candidates.
- We rely on trade secret protection to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.
- Our management team has significant experience in cell processing and commercial-scale cellular therapy manufacturing. Leveraging this experience, we are building our global network of suppliers and CMO partners which combines their expertise in vector manufacturing with a closed, automated manufacturing system, all utilizing cGMP.
- Our gene therapies are designed to potentially provide a curative benefit. If our gene therapies are approved before any other potentially curative treatments, we believe the benefits of our approach and the resulting first mover advantage may provide meaningful disincentive for companies seeking to develop potentially curative therapies that may compete with our own. See "—Competition."
- We are developing therapies to treat rare diseases and expect to pursue orphan-drug designation in the United States and similar protection outside of the United States. To date, the FDA and the European Commission, or the EC, have each granted orphan drug designation, or ODD, to AVR-RD-02 for the treatment of Gaucher disease, AVR-RD-04 for the treatment of cystinosis, and the FDA has granted ODD to AVR-RD-05 for the treatment of Hunter disease. These and other regulatory exclusivities, if granted or applicable, can prevent competitors, during the exclusivity period, from obtaining regulatory approval of the same drug or biological product for the same indication. See "—Government Regulation."
- We currently in-license patents and patent applications relating to certain of our product candidates. We have also filed our own patent applications, which are positioned to further protect certain of our product candidates.

We have in-licensed patents and patent applications from BioMarin Pharmaceutical Inc., Papillon Therapeutics, Inc. (previously GenStem Therapeutics, Inc.) and The University of Manchester directed to compositions and methods related to the manufacture and use of certain of our gene therapies. In addition, we have in-licensed certain intellectual property rights and know-how from the University Health Network and affiliates of Lund University. For example, we have in-licensed know-how and data from University Health Network related to AVR-RD-01, our Fabry disease program which was deprioritized in January 2022. Also for example, we have in-licensed know-how and data related to AVR-RD-02, including certain information about the vector and its use, from certain academic scientists affiliated with Lund University. Each of our licenses are limited to particular fields, such as Gaucher disease, cystinosis, Hunter syndrome, Pompe disease, or Fabry disease, and are subject to certain retained rights. We do not control the prosecution and maintenance of all of our in-licensed patents and patent applications, and our rights to enforce the patents are limited in certain ways. For additional detail regarding the risks associated with our license agreements see "*Risk Factors—Risks Related to Intellectual Property.*"

As of March 1, 2023, our in-licensed patent portfolio relating to certain of our gene therapies included the following:

- *AVR-RD-03 (Pompe program)*: one U.S. patent, projected to expire in 2023, and one U.S. patent application, which if granted, would be projected to expire in 2029, as well as corresponding patents and patent applications in certain foreign jurisdictions, as they pertain to compositions and methods for promoting lysosomal uptake of acid alpha-glucosidase and the treatment of Pompe disease. These patents and patent applications are licensed to us by BioMarin and relate to the GILT tag.
- *AVR-RD-04 (Cystinosis program)*: one U.S. patent application, which, if granted, would be projected to expire in 2038, as well as corresponding patents and patent applications in certain foreign jurisdictions, containing claims directed to hematopoietic stem cells expressing cystinosin and methods of using the same for the treatment of cystinosis. These patent applications are licensed to us by Papillon Therapeutics (formerly GenStem Therapeutics), and Papillon obtained its rights from the University of California, San Diego.
- *AVR-RD-05 (Hunter program)*: two U.S. patent applications, which, if granted, would be projected to expire in 2038, as well as corresponding patents and patent applications in certain foreign jurisdictions, containing claims directed to gene therapy vectors encoding iduronate-2-sulfatase and methods of using the same for the treatment of Hunter syndrome. These patent applications are licensed to us by the University of Manchester.

As of March 1, 2023, our Company-owned patent portfolio also included the following:

- *AVR-RD-03 (Pompe program)*: one international (PCT) application, which, if granted in the U.S., would be projected to expire in 2041, containing claims directed to CD34+ stem cells expressing acid alpha-glucosidase and methods of using the same for the treatment of Pompe disease.

The term of any given patent depends upon the legal term of patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the application, subject to the timely payment of maintenance fees, among other considerations. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office, or USPTO, in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed commonly owned patent. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of FDA regulatory review period. However, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. In certain foreign jurisdictions similar extensions as compensation for regulatory delays are also available. The actual protection afforded by a patent varies on a claim by claim and country by country basis for each applicable product and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. Currently, we do not own or license patents or patent applications related to our AVR-RD-01 (which we deprioritized in January 2022), AVR-RD-02, or AVR-RD-06 product candidates. We rely, in some circumstances, on trade secrets and unpatented know-how that is either owned by or licensed to us to protect our technology. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors.

License Agreements

License Agreement with The University of Manchester

In September 2020, we entered into an agreement, or the MPSII License Agreement, with The University of Manchester, whereby UoM granted us an exclusive worldwide license under certain patent and other intellectual property rights, subject to certain retained rights, to develop, commercialize and sell an *ex vivo* lentiviral gene therapy for use in the treatment of Hunter syndrome, or mucopolysaccharidosis type II. As consideration for the MPSII License Agreement, we agreed to pay UoM an upfront, one-time fee of $8.0 million.

As part of the agreement, we are obligated to make milestone payments of up to an aggregate of $80.0 million upon the achievement of specified development and regulatory milestones, to pay royalties, on a product-by-product and country-by-country basis, of a mid-single digit percentage based on net sales of products licensed under the agreement and to pay a low double-digit percentage of any sublicense fees received by us. In the third quarter of 2022, we paid a $2.0 million milestone under the MPSII License Agreement following regulatory approval of the CTA for the collaborator-sponsored Phase 1/2 clinical trial sponsored by UoM, and the next anticipated payment milestone is $4.0 million, upon the dosing of the first patient in the collaborator-sponsored Phase 1/2 clinical trial sponsored by UoM, which payment is anticipated in the second half of 2023.

Unless terminated earlier, the agreement expires upon the later of 15 years from the effective date or the expiration of the last valid claim of the licensed patents, subject to certain surviving rights and obligations. We and UoM can each terminate the agreement in the event of the bankruptcy or insolvency of the other party, or a material breach by the other party and failure to cure such breach within a certain period of time. UoM has the right to terminate the agreement in the event of certain actions relating to challenge or opposition to the licensed intellectual property brought us or its affiliates or sublicensees.

Concurrently with the MPSII License Agreement, we entered into a collaborative research funding agreement with UoM, or the CRFA. Under the CRFA, we have agreed to fund the budgeted costs of an investigator-sponsored Phase 1/2 clinical trial to be sponsored by UoM in connection with the development activities under the MPSII License Agreement, which are currently estimated to equal approximately £9.9 million in the aggregate.

Exclusive License Agreement with University Health Network

In November 2016, we entered into a license agreement with University Health Network, or UHN, pursuant to which UHN granted us an exclusive worldwide license under certain intellectual property rights and a non-exclusive worldwide license under certain know-how, including certain rights to data, in each case subject to certain retained rights, to develop, commercialize and sell products for use in the treatment of Fabry disease. Intellectual property licensed to us under this agreement relates to our Fabry program, which we deprioritized in January 2022. Under the terms of the agreement, we are required to meet certain performance milestones within specified timeframes. UHN may terminate the agreement if we fail to meet these performance milestones despite using commercially reasonable efforts and we are unable to reach agreement with UHN on revised timeframes.

As consideration for the licenses, we paid to UHN a one-time upfront fee in the amount of CAD$75,000 and are obligated to pay an additional annual fee until the first sale of a licensed product in certain markets. We are also required to make payments to UHN in connection with the achievement of certain development and regulatory milestones, in an aggregate amount of CAD$2.45 million, as well as royalties on a country-by-country basis of a low to mid-single digit percentages on annual sales of licensed products and a lower single digit royalty in certain circumstances. Additionally, we agree to pay a low double-digit percentage of all sublicensing revenue. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration or termination of the last valid claim under the licensed patent rights in such country (if and when any such patent rights come into existence under the license agreement in the future), the tenth anniversary of the first commercial sale of such licensed product in such country and the expiration of any applicable regulatory exclusivity in such country.

In addition, under this agreement we made a philanthropic commitment to donate funds to organizations for the benefit of the Canadian Fabry community in an amount equal to a low double-digit percentage of our royalty payments and regulatory milestone payments, up to a maximum amount of CAD$0.5 million in any calendar year.

Unless terminated earlier, this exclusive license agreement with UHN will expire upon the expiration of our royalty obligation for all licensed products. Either we or UHN may terminate the license agreement if the other party commits a material breach and fails to cure such breach within a certain period of time. UHN may terminate this agreement if we enter into bankruptcy or insolvency. We may terminate this agreement for any reason upon notice to UHN.

License Agreement with Lund University Rights Holders

In January 2017, we entered into an exclusive license agreement with Prof. Stefan Karlsson and Dr. Maria Dahl, affiliates of Lund University, pursuant to which Prof. Karlsson and Dr. Dahl, and certain other relevant rights holders that may have an interest in intellectual property generated under a research project we are funding with Lund University, granted to us an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights to develop, commercialize and sell products in any and all uses relevant to Gaucher disease. Intellectual property licensed to us under this agreement relates to our Gaucher program.

As consideration for the license, we are required to make payments in connection with the achievement of certain milestones up to an aggregate of $0.55 million.

Our license agreement with the rights holders expires on the latest of (i) the twentieth anniversary of the end of a certain research project we are funding pursuant to an agreement with Lund University, (ii) the expiration of the term of any patent filed on the licensed rights that covers a licensed product, (iii) the expiration of any applicable marketing exclusivity right and (iv) such time that neither we nor any of our sublicensees or partners or contractors are commercializing a licensed product. Either we or the rights holders acting together may terminate the license agreement if the other such party commits a material breach and fails to cure such breach within a certain period of time, or if the other party enters into liquidation, becomes insolvent, or enters into composition or statutory reorganization proceedings.

License Agreement with BioMarin Pharmaceutical Inc.

In August 2017, we entered into a license agreement with BioMarin pursuant to which BioMarin granted us an exclusive worldwide license under certain intellectual property rights related to GILT tags owned or controlled by BioMarin to develop, commercialize and sell retroviridae-based gene therapy products for use in the treatment of Pompe disease. This agreement was amended in February 2018 and again in January 2020 to, among things, provide that BioMarin would supply us with certain materials related to the GILT tags technology. Under the terms of the agreement, we must use commercially reasonable efforts to develop and commercialize one or more licensed products in the United States and certain European countries. In addition, we are required to initiate an IND-enabling pharmacology/toxicology study of a licensed product within a specified period of time.

As consideration for the license, we paid an initial license fee in the amount of $0.5 million and issued 233,765 shares of our Series B preferred stock to BioMarin at the time of our Series B financing. We are also obligated to make payments to BioMarin upon achievement of certain milestones up to an aggregate of $13.0 million and pay to BioMarin a low single digit royalty percentage on net sales of licensed products covered by patent rights in a relevant country. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration or termination of the last valid claim under the licensed patent rights in such country, which is currently projected to occur in 2029, the tenth anniversary of the first commercial sale of such licensed product in such country and the expiration of any applicable regulatory exclusivity in such country.

Unless terminated earlier, our license agreement with BioMarin will expire upon the expiration of our royalty obligation for all licensed products throughout the world. Either we or BioMarin may terminate the license agreement if the other party commits a material breach and fails to cure such breach within a certain period of time. BioMarin may also terminate the agreement in the event of any challenge or opposition to the licensed patent rights or related actions brought by us or our affiliates or sublicensees, or if we, our affiliates or sublicensees knowingly assist a third party in challenging or otherwise opposing the licensed patent rights, except as required under a court order or subpoena. In addition, BioMarin may terminate the agreement upon our bankruptcy or insolvency. We may terminate the agreement for any reason upon notice to BioMarin.

License Agreement with Papillon Therapeutics, Inc. (previously GenStem Therapeutics, Inc.)

In October 2017, we entered into a license agreement with GenStem Therapeutics, Inc., or GenStem, pursuant to which GenStem granted us an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights owned or controlled by GenStem related to our cystinosis program, including certain rights licensed to GenStem from the University of California, San Diego, to develop, commercialize and sell products for use in the treatment of cystinosis. Under the terms of the agreement, we must use commercially reasonable efforts to develop and commercialize one or more licensed products in the United States and in at least one country from other specified markets. We also agreed to comply with certain access requirements consistent with the California Institute for Regenerative Medicine regulations and to manufacture certain licensed products substantially in the United States. In October 2021, we received noticed that the license agreement with GenStem had been assigned to Papillon Therapeutics, Inc., or Papillon.

As consideration for the license, we paid an initial license fee in the amount of $1.0 million and are required to make payments upon completion of certain development milestones up to an aggregate of $16.0 million. For example, in November 2019 we made a $2.0 million payment in connection with the dosing of the first patient in the investigator-sponsored Phase 1/2 clinical trial of AVR-RD-04 in cystinosis in the United States. Additionally, we will pay to Papillon a tiered mid to high-single digit royalty percentage on annual net sales of licensed products as well as a low double-digit percentage of sublicense income received from certain third party sublicensees. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis on the eleventh anniversary of the first commercial sale of such licensed product in such country or the expiration of the last valid claim under the licensed patent rights covering such licensed product in such country, which is currently projected to occur in 2038, whichever is later.

Unless terminated earlier, our license agreement with Papillon will terminate upon the expiration of our royalty obligation for all licensed products throughout the world. Either we or Papillon may terminate the license agreement if the other party commits a material breach and fails to cure such breach within a certain period of time. In addition, we may terminate the agreement for any reason upon notice to Papillon.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. Our potential competitors include larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as academic institutions, government agencies and private and public research institutions. Key competitive factors affecting the commercial success of our gene therapies are likely to be efficacy, safety and tolerability profile, reliability, convenience, price and reimbursement.

The market for treatment of lysosomal disorders is especially large and competitive. The gene therapies we are currently developing, if approved, will face competition.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA approval for drugs and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product we may commercialize and may render our gene therapies obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our gene therapies. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. Finally, the development of new treatment methods for the diseases we are targeting could render our gene therapies non-competitive or obsolete. See "Risk Factors—Risks related to the discovery and development of our product candidates—We face significant competition in our industry and there can be no assurance that our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates," and elsewhere in this Annual Report on Form 10-K for more information regarding competitors and competitive products.

Government Regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. Each clinical study protocol for a gene therapy product must be reviewed by the FDA, and FDA approval must be obtained before the marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in INDs for gene therapies.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products 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.

U.S. Biological Products Development Process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;

- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- approval by an independent institutional review board, or IRB, or ethics committee at each clinical study site before each study may be initiated;
- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a Biologics License Application, or BLA, for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with cGMPs, to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or GTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. An IND is a request for authorization from the FDA to ship an unapproved, investigational product in interstate commerce and to administer it to humans, and must become effective before clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. In addition to the submission of an IND to the FDA before initiation of a clinical trial in the United States, certain human clinical trials involving recombinant or synthetic nucleic acid molecules are subject to oversight of institutional biosafety committees, or IBCs, as set forth in the National Institutes of Health, or NIH, Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. Under the NIH Guidelines, recombinant and synthetic nucleic acids are defined as: (i) molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell (i.e., recombinant nucleic acids); (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (i.e., synthetic nucleic acids); or (iii) molecules that result from the replication of those described in (i) or (ii). Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an 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.

The FDA also may impose clinical holds on a biological product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Clinical studies involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an IRB at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed. Clinical research involving recombinant DNA that is subject to NIH guidelines also must be reviewed by an institutional biosafety committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

Clinical studies typically are conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *Phase 2*. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- *Phase 3*. Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for approval and product labeling.

Post-approval clinical studies, sometimes referred to as Phase 4 clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators. Annual progress reports detailing the results of the clinical studies must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical studies may not be completed successfully within any specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical study at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical study at its institution if the clinical study is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical studies, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. Review and Approval Processes

After the completion of clinical studies of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. In most cases, the submission of a BLA is subject to a substantial application user fee, although the fee may be waived under certain circumstances. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original BLAs, the FDA has ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. The FDA does not always meet its PDUFA goal dates, and the review process is often significantly extended by FDA requests for additional information or clarification. This review typically takes twelve months from the date the BLA is submitted to the FDA because the FDA has approximately two months to make a “filing” decision. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product’s identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved 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. During the biological product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with GTPs. These are FDA regulations 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. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure cGMP, GTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA for a novel product (e.g., new active ingredient, new indication, etc.) must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical studies, sometimes referred to as Phase 4 clinical studies, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited Development and Review Programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic

may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

Under the breakthrough therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible.

Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Under priority review, the FDA’s goal is to review an application in six months, compared to ten months for a standard review.

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical studies establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical studies. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA is now permitted to require, as appropriate, that such trials be underway prior to approval or within a specific time period after the date of approval for a product granted accelerated approval. Sponsors are also required to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. Under FDORA, the FDA has increased authority for expedited procedures to withdraw approval of a drug or indication approved under accelerated approval if, for example, the sponsor fails to conduct such studies in a timely manner and send the necessary updates to the FDA, or if a confirmatory trial fails to verify the predicted clinical benefit of the product. In addition, for products being considered for accelerated approval, the FDA generally requires, unless otherwise informed by the agency, that all advertising and promotional materials intended for dissemination of publication within 120 days of marketing approval be submitted to the agency for review during the pre-approval review period.

Regenerative Medicine Advanced Therapies Designation

As part of the 21st Century Cures Act, enacted in December 2016, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of regenerative medicine advanced therapies, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Regenerative medicine advanced therapies do not include those human cells, tissues, and cellular and tissue based products regulated solely under section 361 of the Public Health Service Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that the FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. The FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with the FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. Like the FDA's other expedited development programs, RMAT designation does not change the standards for approval but may expedite the development or approval process.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to cGMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the cGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the

manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products, and those supplying products, ingredients, and components of them, 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 cGMPs and other laws. Manufacturers and other parties involved in the drug supply chain for prescription drug products must also comply with product tracking and tracing requirements and for notifying the FDA of counterfeit, diverted, stolen and intentionally adulterate products or products that are otherwise unfit for distribution in the United States. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some 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, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our patents, if and as applicable, to add patent life beyond its current expiration date, depending on the expected length of the clinical studies and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The ACA, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously

administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biological product is granted four- and 12-year exclusivity periods from the time of first licensure of the product. 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, and FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. "First licensure" typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the "first licensure" of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

Additional Regulation

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

U.S. Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Government Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the European Union, for example, a CTA must be submitted for each clinical trial to each participating country's national health authority and an independent ethics committee, much like the FDA and an IRB, respectively. Under the new Clinical Trials Regulation (EU) No 536/2014, which replaced the Clinical Trials Directive 2001/20/EC on January 31, 2022, a single application is now made through the Clinical Trials Information System, or CTIS, for clinical trial authorization in up to 30 EU/EEA countries at the same time and with a single set of documentation. The assessment of applications for clinical trials is divided into two parts (Part I contains scientific and medicinal product documentation and Part II contains the national and patient-level documentation). Part I is assessed by a coordinated review by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned) of a draft report prepared by a

Reference Member State. Part II is assessed separately by each Member State concerned. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State, however overall related timelines are defined by the Clinical Trials Regulation. The new Clinical Trials Regulation also provides for simplified reporting procedures for clinical trial sponsors.

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

To obtain regulatory approval of a product in the European Union, we must submit a marketing authorization application. The centralized procedure for marketing authorization in the European Union is mandatory for certain types of products, such as products produced by biotechnological processes, orphan medicinal products, advanced-therapy medicinal products (gene-therapy, somatic cell-therapy or tissue-engineered medicines) and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the European Union, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the European Union. A centralized marketing authorization is issued by the EC through the centralized procedure, based on the opinion of the Committee for Medicinal Products for Human Use (CHMP), of the EMA, and is valid throughout the entire territory of EU and the additional Member States of the European Economic Area (Iceland, Liechtenstein and Norway), or EEA.

The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products approved on the basis of a complete and independent data package generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from referencing the innovator's preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization in the European Union, for a period of eight years from the date on which the reference product was first authorized in the European Union. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Even if an innovative medicinal product gains the prescribed period of data exclusivity, another company could nevertheless also market another version of the product if such company obtained an marketing authorization based on an application with a complete and independent data package of pharmaceutical tests, preclinical tests and clinical trials.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, is unlikely to generate sufficient return in the European Union to justify the necessary investment in its development; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication, during which a marketing authorization may not be granted in the European Union for a "similar medicinal product" to the authorized orphan product.

The 10-year market exclusivity may 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 designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar medicinal product for the same indication as an authorized orphan product at any time if:

- The second applicant can establish that its product, although similar to the authorized orphan product, is safer, more effective or otherwise clinically superior;
- The marketing authorization holder for the authorized orphan product consents to a second orphan medicinal product application; or
- The marketing authorization holder for the authorized orphan product cannot supply enough orphan medicinal product.

The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The UK officially withdrew from the European Union on January 31, 2020 and the EU and the UK signed a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not provide for wholesale mutual recognition of UK and European Union pharmaceutical regulations. At present, Great Britain has implemented European Union legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the European Union regulatory framework continues to apply in Northern Ireland). The regulatory regime in Great Britain therefore aligns in many ways with current European Union regulations, however it is possible that these regimes will diverge more significantly in the future now that Great Britain's regulatory system is independent from the European Union. For example, the UK has implemented the now repealed Clinical Trials Directive 2001/20/EC into national law through the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). The extent to which the regulation of clinical trials in the UK in the future will mirror the new Clinical Trials Regulation now that has come into effect is not yet known, however the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK's medicines regulator, has conducted a consultation on a set of proposals designed to improve and strengthen the UK clinical trials legislation. Such consultation ran from January 17, 2022 to March 14, 2022, and the MHRA is currently analyzing feedback.

Great Britain is no longer covered by the European Union's procedures for the grant of marketing authorizations (Northern Ireland is covered by the centralized authorization procedure for the time being). A separate marketing authorization is therefore required to market drugs in Great Britain. For three years from January 1, 2021, the MHRA may adopt decisions taken by the European Commission on the approval of new marketing authorizations through the centralized procedure, and the MHRA will have regard to marketing authorizations approved in a country in the EEA (although in both cases a marketing authorization will only be granted if any Great Britain-specific requirements are met). This is known as the EC Decision Reliance Procedure. On January 24, 2023, the MHRA announced that a new international recognition framework will be put in place from January 1, 2024, which will have regard to decisions on the approval of marketing authorizations made by the EMA and certain other regulators.

Since January 1, 2021, a separate process for orphan designation has applied in Great Britain. There is now no pre-marketing authorization orphan designation (as there is in the European Union) in Great Britain and the application for orphan designation will be reviewed by the MHRA at the time of a marketing authorization application for a UK or Great Britain marketing authorization. The criteria for orphan designation are the same as in the European Union, save that they apply to Great Britain only (e.g., there must be no satisfactory method of diagnosis, prevention or treatment of the condition concerned in Great Britain, as opposed to the European Union, and the prevalence of the condition must be no more than 5 in 10,000 persons in Great Britain).

On February 27, 2023, the UK government and the European Commission announced a political agreement in principle to replace the Northern Ireland Protocol with a new set of arrangements, known as the "Windsor Framework". This new framework fundamentally changes the existing system under the Northern Ireland Protocol, including with respect to the regulation of medicinal products in the UK. In particular, the MHRA will be responsible for approving all medicinal products destined for the UK market (Great Britain and Northern Ireland), and the EMA will no longer have any role in approving medicinal products destined for Northern Ireland. Once the Windsor Framework is approved by the EU-UK Joint Committee, the UK Government and the European Union will enact legislative measures to enact it into law.

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

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

Other Healthcare Laws and Compliance Requirements

In addition to FDA restrictions on the marketing of pharmaceutical products, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our business or financial arrangements and relationships through which we market, sell and distribute the gene therapies for which we obtain approval. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity can be found guilty of violating the statute without actual knowledge of the statute or specific intent to violate it. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act, or FCA. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the FCA, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The FCA also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements 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, relating to the privacy, security and transmission of individually identifiable health information. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, or HHS, information related to payments or other transfers of value made to physicians (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain other licensed health practitioners and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare services reimbursed by any source, not just governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines, imprisonment and/or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the U.S. government under the federal False Claims Act as well as under the false claims laws of several states.

Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices, including our arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, may not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our gene therapies outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

If any of the physicians or other healthcare 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 criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business.

Regulators globally are also imposing greater monetary fines for privacy violations. For example, non-compliance with the European Union General Data Protection Regulation, or GDPR, may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher.

European and UK Personal Data Collection

The collection and use of personal health data in the European Union is governed by the provisions of the GDPR. The GDPR applies to any company established in the European Union as well as to those outside the European Union if they collect and use personal data in connection with the offering of goods or services to individuals in the European Union or the monitoring of their behavior. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of information, mandatory data breach notification requirements and onerous new obligations on services providers. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of personal data, such as healthcare data or other sensitive information, could greatly increase our cost of providing our products and services or even prevent us from offering certain services in jurisdictions that we may operate in.

In addition, further to the UK's exit from the EU on January 31, 2020, the GDPR (as it existed on December 31, 2020 but subject to certain UK specific amendment) was incorporated into UK law pursuant to the UK's European Union (Withdrawal) Act, or the UK GDPR. The UK GDPR and the UK Data Protection Act 2018 set out the UK's data protection regime, which is independent from but currently still aligned to the EU's data protection regime. It is possible that over time the GDPR and the UK GDPR will diverge further. The UK government has announced plans to reform the data protection legal framework in the UK in its Data Reform Bill but this is not yet in final form. This lack of clarity on future UK laws and regulations and their interaction with EU laws and regulations could add legal risk, uncertainty, complexity and cost to our handling of personal information and our privacy and data security compliance programs and could require us to implement different compliance measures for the UK and the EU. Non-compliance with the UK GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in 2010, the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjects drug manufacturers to annual fees based on pharmaceutical companies' share of sales to federal healthcare programs; created 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 established the Center for Medicare Innovation at Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

In addition, other legislative and regulatory changes have been proposed and adopted in the United States since the ACE was enacted:

- The Budget Control Act of 2011 and subsequent legislation, among other things, created measures for spending reductions by Congress that include aggregate reductions of Medicare payments to providers of 2% per fiscal year, which remain in effect through 2031. Due to the Statutory Pay-As-You-Go Act of 2010, estimated budget deficit increases resulting from the American Rescue Plan Act of 2021, and subsequent legislation, Medicare payments to providers will be further reduced starting in 2025 absent further legislation

- The U.S. American Taxpayer Relief Act of 2012 further reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayment to providers from three to five years.

- On April 13, 2017, CMS published a final rule that gives states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

- On May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA -approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

- On May 23, 2019, CMS published a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, and review the relationship between pricing and manufacturer patient programs. The Inflation Reduction Act of 2022, or IRA includes several provisions that may impact our business to varying degrees, including provisions that reduce the out-of-pocket spending cap for Medicare Part D beneficiaries from $7,050 to $2,000 starting in 2025, thereby effectively eliminating the coverage gap; impose new manufacturer financial liability on certain drugs under Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D price caps for certain high-cost drugs and biologics without generic or biosimilar competition; require companies to pay rebates to Medicare for certain drug prices that increase faster than inflation; and delay until January 1, 2032 the implementation of the HHS rebate rule that would have limited the fees that pharmacy benefit managers can charge. Further, under the IRA, orphan drugs are exempted from the Medicare drug price negotiation program, but only if they have one rare disease designation and for which the only approved indication is for that disease or condition. If a product receives multiple rare disease designations or has multiple approved indications, it may not qualify for the orphan drug exemption. The effects of the IRA on our business and the healthcare industry in general is not yet known.

In addition, President Biden has issued multiple executive orders that have sought to reduce prescription drug costs. In February 2023, HHS also issued a proposal in response to an October 2022 executive order from President Biden that includes a proposed prescription drug pricing model that will test whether targeted Medicare payment adjustments will sufficiently incentivize manufacturers to complete confirmatory trials for drugs approved through FDA's accelerated approval pathway. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that they will continue to seek new legislative measures to control drug costs.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical 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.

We expect that additional foreign, federal and state healthcare reform measures will be adopted in the future, any of which could limit the amounts that foreign federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, if approved, or additional pricing pressures.

Coverage and Reimbursement

While there have been some HSC gene therapies that have obtained coverage and reimbursement, significant uncertainty exists as to the coverage and reimbursement status of any gene therapies for which we obtain regulatory approval. In the United States and markets in other countries, sales of any gene therapies for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a third-party payor not to cover our gene therapies could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Moreover, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In addition, coverage and reimbursement for products can differ significantly from payor to payor. One third-party payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate.

As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor separately and will be a time-consuming process. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price, or ASP, and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain and maintain coverage and reimbursement for any product, we may need to conduct expensive clinical trials in order to demonstrate the medical necessity and cost-effectiveness of such product, in addition to the costs required to obtain regulatory approvals. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, 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 therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures.

Employees and Human Capital Resources

As of December 31, 2022, we had 78 full-time employees, 17 of whom have Ph.D. or M.D. degrees. Of these full-time employees, 52 employees are engaged in research and development activities and 26 employees are engaged in finance, legal, human resources, facilities and general management. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, retaining, incentivizing and integrating existing and new employees, and identifying and recruiting prospective new employees. The principal purposes of our incentive plans are to

attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards and cash-based performance bonus awards.

Available Information

We are subject to the informational requirements of the Exchange Act and are required to file annual, quarterly and current reports, proxy statements and other information with the SEC. You can read our SEC filings at the SEC's website at www.sec.gov. We also maintain a website at www.avrobio.com. You may access, free of charge, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and any amendments to those reports, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. You should carefully consider the following risks and uncertainties, together with all other information in this Annual Report on Form 10-K, including our consolidated financial statements and related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," as well as our other filings with the Securities and Exchange Commission, or the SEC, before investing in our common stock. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations. The market price of our common stock could decline if one or more of these risks or uncertainties were to occur, which may cause you to lose all or part of the money you paid to buy our common stock. Additional risks that are currently unknown to us or that we currently believe to be immaterial may also impair our business. Certain statements below are forward-looking statements. See "Forward-Looking Information" in this Annual Report on Form 10-K.

Risks related to our business, financial position and need for additional capital

We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred net losses. We incurred net losses of $105.9 million and $119.1 million for the years ended December 31, 2022 and 2021, respectively. We historically financed our operations primarily through private placements of our preferred stock and, more recently, our initial public offering and follow-on public offerings of our common stock, as well as sales of our common stock under our "at-the-market" facility. In addition, on November 2, 2021 we entered into the Loan and Security Agreement, or the Term Loan Agreement, by and among the Company, the lenders party thereto from time to time and Silicon Valley Bank (or its successor bridge bank), which we refer to as SVB. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development of our product candidates, as well as assembling our team. We expect that it will be several years, if ever, before we have commercialized any product candidates. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if, and as, we:

- continue our development of our product candidates, including continuing enrollment in our ongoing clinical trials, particularly if and as we commence and continue clinical-stage activities for our product candidates;
- initiate additional clinical trials and preclinical studies for our current and future product candidates, if any;
- experience delays or interruptions in preclinical studies, clinical trials, or our supply chain due to the ongoing COVID-19 pandemic;
- seek to identify and develop or in-license additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- continue our implementation of our plato platform as we seek to industrialize our HSC gene therapy approach into a robust, scalable and, if approved, commercially viable process;
- hire and retain additional personnel, such as clinical, quality control, regulatory and scientific personnel;
- expand our office space, infrastructure and facilities as needed to accommodate our employee base, including adding equipment and physical infrastructure to support our research and development; and
- continue to incur additional public company-related costs.

To become and remain profitable, we must develop and eventually commercialize product candidates with significant market potential and acceptance. This will require us to be successful in a range of challenging activities, and our expenses will increase substantially as we seek to initiate, conduct and complete preclinical and clinical trials of our product candidates, and manufacture, market and sell these or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our Company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our Company also could cause you to lose all or part of your investment.

Management identified certain conditions or events, which, considered in the aggregate, raise substantial doubt about our ability to continue as a going concern and the future viability of the Company, including the risk that we will be unable to raise adequate additional capital to fund our operations. Substantial doubt about our ability to continue as a going concern and the Company's inability to raise adequate capital as and when needed may create negative reactions to the price of our common stock and could have a negative impact on our financial condition and ability to pursue our business strategies. There can be no assurance that our current operating plan will be achieved or that additional funding will be available on terms acceptable to us, or at all. If we are unable to raise additional capital at levels sufficient to fund our operations or on terms acceptable to us, we will need to consider other various strategic alternatives, including a merger, reverse merger, sale, wind-down, liquidation and dissolution or other strategic transaction, or be unable to continue operations. Further, if we are unable to continue as a going concern, we may have to liquidate our assets and the values we receive for our assets in liquidation or dissolution could be significantly lower than the values reflected in our consolidated financial statements.

We have never generated revenue from product sales and do not expect to do so for the next several years, if ever.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. We do not anticipate generating revenues from product sales for the next several years, if ever. Our ability to generate future revenues from product sales depends heavily on our, or our collaborators', success in:

- completing research and preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical trials;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by establishing a sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- qualifying for adequate coverage and reimbursement by government and third-party payors for our product candidates;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and the commercial market demand for our product candidates, if approved;
- obtaining market acceptance of our product candidates, if approved, as a viable treatment option;
- 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 under such arrangements; and
- attracting, hiring and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA or other foreign regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

As of December 31, 2022, we had cash and cash equivalents of $92.6 million. We believe that our existing cash and cash equivalents as of December 31, 2022 will enable us to fund our operating expenses and capital expenditure requirements into the first quarter of 2024. This forecast of cash resources is forward-looking information that involves risks and uncertainties, and the actual amount of our expenses could vary materially and adversely as a result of a number of factors. We have based our estimates on assumptions that may prove to be wrong, and our expenses could prove to be significantly higher than we currently anticipate.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and continue to enhance and optimize our vector technology and manufacturing processes. Furthermore, we currently have a total of four gene therapy programs in our pipeline, two of which are in clinical development. Further development of these programs will require us to expend significant resources to advance these candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution. Furthermore, we expect to continue to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on reasonable terms, we would be forced to delay, reduce or eliminate certain of our research and development programs. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our current and future product candidates, including the extent of any impacts from the ongoing COVID-19 pandemic on these activities;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of future activities, including product sales, medical affairs, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers;
- revenue, if any, received from commercial sale of our products, should any of our product candidates receive marketing approval;
- the amounts, if any, raised from potential financings and capital raising activities;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs of defending against and resolving adverse litigation, if any;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

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 product revenues, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Our Term Loan Agreement contains restrictions that potentially limit our flexibility in operating our business, and we may be required to make a prepayment or repay our outstanding indebtedness earlier than we expect. In addition, as a result of the deprioritization of our Fabry program, we can no longer draw $20.0 million of term loans that were contingent upon the achievement of certain milestones related to our development of AVR-RD-01 for Fabry disease.

On November 2, 2021, we entered into the Term Loan Agreement. The Term Loan Agreement provided for term loans of up to $65.0 million in the aggregate available in three tranches, but due to the deprioritization of our Fabry program we can no longer draw $20.0 million of term loans that were contingent upon the achievement of certain milestones related to our development of AVR-RD-01 for Fabry disease. As a result, the amount that remains available to us for future drawdown, subject to satisfaction of the conditions in the Term Loan Agreement, is $30.0 million, $15.0 million of which requires the consent of the Agent and Lenders. The Term Loan Agreement contains various covenants that limit our ability to engage in specified types of transactions. These covenants limit our ability to, among other things:

- incur or assume certain debt;
- merge or consolidate or acquire all or substantially all of the capital stock or property of another entity;
- change the nature of our business;
- change our organizational structure or type;

- license, transfer, or dispose of certain assets;
- grant certain types of liens on our assets;
- make certain investments;
- maintain operating accounts, depository accounts and excess cash at institutions other than SVB;
- pay cash dividends; and
- enter into material transactions with affiliates.

A breach of any of these covenants could result in an event of default under the Term Loan Agreement. An event of default will also occur if, among other things, a material adverse change in our business, operations, or condition occurs, which could potentially include a material impairment of the prospect of our repayment of any portion of the amounts we owe under the Term Loan Agreement. In the case of a continuing event of default under the Term Loan Agreement, the lenders could elect to declare all amounts outstanding to be immediately due and payable, proceed against the collateral in which we granted the Lenders a security interest under the Term Loan Agreement, or otherwise exercise the rights of a secured creditor. Amounts outstanding under the Term Loan Agreement are secured by all of our existing and future assets, excluding intellectual property, which is subject to a negative pledge arrangement.

At closing, we drew $15.0 million of the $30.0 million available to us as part of the first tranche. As executed, the Term Loan Agreement also provided the ability to access up to an additional $35.0 million, of which $20.0 million could be drawn in two additional tranches subject to the achievement of certain regulatory and clinical milestones, or the Milestone Funding, and of which $15.0 million could be drawn in an additional tranche with the approval of the Agent and the Lenders. However, as a result of the deprioritization of our Fabry disease program, we are no longer able to draw the $20.0 million of Milestone Funding per the terms of the Term Loan Agreement. Moreover, if the Agent and Lenders do not consent, we would not be able to draw down the final $15.0 million tranche of financing. If we are unable to access the final $15.0 million tranche, there can be no assurance that we will be able to obtain alternative financing to replace such tranche on commercially reasonable terms or at all, which could adversely impact our business.

We may not have enough available cash to repay or refinance our indebtedness at the time any such repayment is required. In such an event, we may be required to delay, limit, reduce, or terminate our preclinical and clinical product development or grant others rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. Our business, financial condition, and results of operations could be materially adversely affected as a result. For further risks related to indebtedness, see “Risk Factors—Risks related to our business, financial position and need for additional capital—Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults, or non-performance by financial institutions or transactional counterparties, could adversely affect the Company’s current and projected business operations and its financial condition and results of operations.”

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or cause us to relinquish valuable rights.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity, convertible debt securities or other equity-based derivative securities, your ownership interest will be diluted and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. Any additional indebtedness we incur would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our common stock to decline and existing stockholders may not agree with our financing plans or the terms of such financings. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, or our product candidates, or grant licenses on terms unfavorable to us. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

We are a clinical-stage company founded in November 2015. Our operations to date have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring rights to our technology, identifying potential product candidates, undertaking preclinical studies and planning and supporting clinical trials of certain of our

product candidates and establishing research and development and manufacturing capabilities. We have not yet demonstrated the ability to complete clinical trials of our product candidates, obtain marketing approvals, manufacture products on a commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history. In addition, as an early-stage company, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors.

Adverse developments affecting the financial services industry, such as actual events or concerns involving liquidity, defaults, or non-performance by financial institutions or transactional counterparties, could adversely affect the Company's current and projected business operations and its financial condition and results of operations.

Actual events involving limited liquidity, defaults, non-performance or other adverse developments that affect financial institutions, transactional counterparties or other companies in the financial services industry or the financial services industry generally, or concerns or rumors about any events of these kinds or other similar risks, have in the past and may in the future lead to market-wide liquidity problems. For example, on March 10, 2023, SVB was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation, or the FDIC, as receiver. Similarly, on March 12, 2023, Signature Bank and Silvergate Capital Corp. were each swept into receivership. Although a statement by the Department of the Treasury, the Federal Reserve and the FDIC indicated that all depositors of SVB would have access to all of their money after only one business day of closure, including funds held in uninsured deposit accounts, borrowers under credit agreements, letters of credit and certain other financial instruments with SVB, Signature Bank or any other financial institution that is placed into receivership by the FDIC may be unable to access undrawn amounts thereunder. In addition, if any of our contract organizations, vendors, suppliers or other parties with whom we conduct business are unable to access funds pursuant to their own arrangements with such a financial institution, such parties' ability to perform their obligations could be adversely affected. In this regard, counterparties to SVB credit agreements and arrangements, and third parties such as beneficiaries of letters of credit (among others), may experience direct impacts from the closure of SVB and uncertainty remains over liquidity concerns in the broader financial services industry. Similar impacts have occurred in the past, such as during the 2008-2010 financial crisis.

We currently maintain a term loan facility with SVB pursuant to the Term Loan Agreement, under which we have drawn down $15.0 million, but we may be unable to draw down on additional funding under such facility due to SVB's closure. As our facility currently requires substantially all of our cash and cash equivalents to be deposited with SVB, historically we have relied primarily on SVB for commercial banking services. We are pursuing actions to make alternative banking arrangements, including opening deposit accounts at one or more other financial institutions. SVB has agreed to waive covenants related to maintaining our deposits at SVB for a period of 30 days, during which time we have agreed to obtain an Account Control Agreement, or ACA, for all accounts held outside of SVB. An ACA is a multi-party agreement among a debtor, lender and a bank that allows the lender to perfect a security interest in the customer's funds by taking control of the deposit account if necessary. However, efforts to open deposit accounts at financial institutions other than SVB may not adequately mitigate the risk of financial crises similar to that experienced by SVB.

Inflation and rapid increases in interest rates have led to a decline in the trading value of previously issued government securities with interest rates below current market interest rates. Although the U.S. Department of Treasury, FDIC and Federal Reserve Board have announced a program to provide up to $25 billion of loans to financial institutions secured by certain of such government securities held by financial institutions to mitigate the risk of potential losses on the sale of such instruments, widespread demands for customer withdrawals or other liquidity needs of financial institutions for immediately liquidity may exceed the capacity of such program. Additionally, there is no guarantee that the U.S. Department of Treasury, FDIC and Federal Reserve Board will provide access to uninsured funds in the future in the event of the closure of other banks or financial institutions, or that they would do so in a timely fashion.

Although we assess our banking relationships as we believe necessary or appropriate, our access to funding sources and other credit arrangements in amounts adequate to finance or capitalize our current and projected future business operations could be significantly impaired by factors that affect our company, the financial institutions with which we have credit agreements or arrangements directly, or the financial services industry or economy in general. These factors could include, among others, events such as liquidity constraints or failures, the ability to perform obligations under various types of financial, credit or liquidity agreements or arrangements, disruptions or instability in the financial services industry or financial markets, or concerns or negative expectations about the prospects for companies in the financial services industry. These factors could involve financial institutions or financial services industry companies with which we have financial or business relationships, but could also include factors involving financial markets or the financial services industry generally.

The results of events or concerns that involve one or more of these factors could include a variety of material and adverse impacts on our current and projected business operations and our financial condition and results of operations. These could include, but may not be limited to, the following:

- Delayed access to deposits or other financial assets or the uninsured loss of deposits or other financial assets;
- Delayed or lost access to, or reductions in borrowings available under revolving existing credit facilities or other working capital sources and/or delays, inability or reductions in the company's ability to refund, roll over or extend the maturity of, or enter into new credit facilities or other working capital resources;
- Potential or actual breach of contractual obligations that require the Company to maintain letters of credit or other credit support arrangements;
- Potential or actual breach of financial covenants in our credit agreements or credit arrangements;
- Potential or actual cross-defaults in other credit agreements, credit arrangements or operating or financing agreements; or
- Termination of cash management arrangements and/or delays in accessing or actual loss of funds subject to cash management arrangements.

In addition, investor concerns regarding the U.S. or international financial systems could result in less favorable commercial financing terms, including higher interest rates or costs and tighter financial and operating covenants, or systemic limitations on access to credit and liquidity sources, thereby making it more difficult for us to acquire financing on acceptable terms or at all. Any decline in available funding or access to our cash and liquidity resources could, among other risks, adversely impact our ability to meet our operating expenses, financial obligations or fulfill our other obligations, result in breaches of our financial and/or contractual obligations or result in violations of federal or state wage and hour laws. Any of these impacts, or any other impacts resulting from the factors described above or other related or similar factors not described above, could have material adverse impacts on our liquidity and our current and/or projected business operations and financial condition and results of operations.

In addition, any further deterioration in the macroeconomic economy or financial services industry could lead to losses or defaults by our contract organizations, vendors, suppliers or other parties with whom we conduct business, which in turn, could have a material adverse effect on our current and/or projected business operations and results of operations and financial condition. For example, contract organizations, vendors, suppliers or other parties with whom we conduct business could be adversely affected by any of the liquidity or other risks that are described above as factors that could result in material adverse impacts on our company, including but not limited to delayed access or loss of access to uninsured deposits or loss of the ability to draw on existing credit facilities involving a troubled or failed financial institution. Any bankruptcy or insolvency involving our contract organizations, vendors, suppliers or other parties with whom we conduct business, or any breach or default by such parties, or the loss of any significant relationships with such parties, could result in a material adverse impact on our business.

Risks related to the discovery and development of our product candidates

Business interruptions resulting from the coronavirus disease, or COVID-19, pandemic or similar public health crises have caused and may continue to cause a disruption of the development of our product candidates and adversely impact our business.

Public health crises such as pandemics or similar outbreaks could adversely impact our business. The COVID-19 pandemic has continued to disrupt normal business operations both in and outside of affected areas and has had significant negative impacts on businesses and financial markets worldwide. We continue to monitor our operations and follow applicable government recommendations, and the majority of our employees, other than our laboratory staff, have adopted a "hybrid" work schedule which generally limits the number of people in our office at any particular time. Notwithstanding these measures, the COVID-19 pandemic, including potential outbreaks of new variants, or any other public health crisis could affect the health and availability of our workforce as well as those of the third parties on which we rely. If members of our management and other key personnel are unable to perform their duties or have limited availability due to COVID-19, we may not be able to execute on our business strategy and/or our operations may be negatively impacted.

In addition, clinical trial activities, including patient enrollment and data collection, are dependent upon global clinical trial sites which were adversely affected by the COVID-19 pandemic. For example, as the global healthcare community responded to the fluctuations in COVID-19 cases and hospitalizations, many hospitals, including our clinical sites, temporarily paused elective procedures, which included dosing of new patients with our investigational gene therapies. While we have resumed data collection and dosing of new patients, our ability to continue clinical activities without further delay or interruption will depend on future developments that are highly uncertain and cannot be accurately predicted.

Additional factors from any public health crisis that may delay or otherwise adversely affect enrollment in or the progress of the clinical trials of our product candidates, as well as our business generally, include:

- the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- limitations on travel that could interrupt key trial activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that may impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials;
- interruption in global shipping affecting the transport of clinical trial materials, such as patient samples, investigational drug product and conditioning drugs and other supplies used in our clinical trials;
- business disruptions caused by workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments and operations, staffing shortages, travel limitations or mass transit disruptions, any of which could adversely impact our business operations or those of third party service providers, contractors, or suppliers on whom we rely, impair the productivity of our personnel, subject us to additional cybersecurity risks, create data accessibility problems, cause us to become more susceptible to communication disruptions, or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors;
- business disruptions involving our third parties on whom we rely, including CROs and other collaborators for the conduct of our clinical trials or our third party suppliers or manufacturers, which could impact their ability to perform adequately or disrupt our supply chain; and
- changes in hospital or research institution policies or government regulations, which could delay or adversely impact our ability to conduct our clinical trials.

Since the beginning of the COVID-19 pandemic, several vaccines for COVID-19 have received Emergency Use Authorization by the FDA and a number of those later received marketing approval. Additional vaccines may be authorized or approved in the future. The resultant demand for vaccines and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials, which could lead to delays in these trials.

These and other factors arising from the COVID-19 pandemic could reemerge or worsen and adversely impact our ability to conduct clinical trials and our business generally, and could have a material adverse impact on our operations and financial condition and results. The extent to which any public health crisis impacts our operations or those of our third party partners will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration of the public health crisis, the efficacy and safety of vaccines, including against emerging variants, the ability of third parties to manufacture and distribute vaccines, among others.

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

We have concentrated our research and development efforts on our HSC gene therapy approach, and our future success depends on our successful development of viable gene therapy product candidates. There can be no assurance that we will not experience problems or delays in developing new product candidates and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. For example, timely enrollment in our clinical trials is dependent upon global clinical trial sites which were and may continue to be adversely affected by the COVID-19 pandemic, especially if a resurgence of cases occurs. In addition, the implementation of our plato platform and upgrades, including our current conditioning regimen or any conditioning regimen we implement in the future, may result in delays or setbacks in our research and development activities, and we may not realize the intended benefits of these efforts. In addition, we may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial, additional or alternative partners, which may prevent us from completing our clinical studies or commercializing our products on a timely or profitable basis, if at all. For example, as of March 20, 2023 we have only dosed ten patients using our plato platform in our clinical trials, which includes six patients in our FAB-GT clinical trial for which we halted enrollment. Our implementation of the LV2 lentiviral vector or of our cell processing to an industrialized, automated closed system using disposable supplies may not be successful or may experience unforeseen delays, which may cause shortages or delays in the supply of our products available for clinical trials and future commercial sales, if any, or impair our research and development efforts, including those in our ongoing and future clinical trials. In addition, there is no assurance that products using our proprietary LV2 lentiviral vector or manufactured using this automated system will ultimately achieve the same favorable preliminary results observed to date. Furthermore, the FDA generally prefers that clinical trials be double-blinded and potentially include sham controls. Such a trial design could be challenging to implement due to the nature of the treatment regimen of HSC gene therapy.

In addition, the clinical trial requirements of the FDA and other foreign regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. To date, only a limited number of HSC gene therapies have received marketing authorization from the FDA or foreign regulatory authorities. 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 the United States, Canada, Europe, Japan or other major markets or how long it will take to commercialize our product candidates, if any are approved. Approvals by foreign regulatory authorities may not be indicative of what the FDA may require for approval, and vice versa.

Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the United States National Institutes of Health, or NIH, also are subject to the NIH Guidelines, under which 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. Before a clinical trial can begin at any institution, that institution's review board, or IRB, and its IBC assesses the safety of the research and identifies any potential risk to public health or the environment. 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. 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 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 any of our product candidates. Similarly, foreign regulatory authorities may issue new guidelines concerning the development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines.

The FDA, NIH and the European Medicines Agency, or EMA, have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. For example, in 2016, the FDA established the Office of Tissues and Advanced Therapies, or OTAT, within the CBER, to consolidate the review of gene therapy and related products, and to advise the CBER on its review. In September 2022, the FDA announced retitling of OTAT to the Office of Therapeutic Products, or OTP, and elevation of OTP to a "Super Office" to meet its growing cell and gene therapy workload. Although FDA has indicated that this change of name and responsibilities is intended to, among other things, increase review capabilities and enhance expertise on new cell and gene therapies, we cannot be certain that this approach will improve the time and cost associated with navigating gene

therapy regulatory requirements, our regulatory strategy or the potential success of our product candidates. Such regulatory action and developments could, instead, delay, impede or even prevent commercialization of some or all of our product candidates.

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 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 certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. 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, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

The FDA continues to develop its approach to assessing gene and cell therapy products. For example, the agency has released a series of draft and final guidance documents relating to, among other topics, various aspects of gene therapy product development, review, and approval, including aspects relating to clinical and manufacturing issues related to gene therapy products. In January 2020, the FDA released a final guidance with recommendations for long-term follow-up studies of patients following human gene therapy administration due to the increased risk of undesirable and unpredictable outcomes with gene therapies that may present as delayed adverse events. We cannot be certain whether such guidance, or other guidance that the FDA may issue, will be relevant to or have an adverse impact on our gene therapy candidates or the duration or expense of any applicable regulatory development and review processes.

Our product candidates and 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.

During the conduct of clinical trials, patients may experience changes in their health, including illnesses, injuries, discomforts or a fatal outcome. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of our product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier clinical trials, as well as conditions that did not occur or went undetected in previous clinical trials, will be reported by patients. Additionally, any early access to the Company's investigational therapies, such as through expanded or Right to Try access or compassionate use, may lead to discovery of undesirable side effects, or other negative consequences that could have adverse impacts on our development programs for current and future product candidates. Gene therapies are also subject to the potential risk that occurrence of adverse events will be delayed following administration of the gene therapy due to persistent biological activity of the genetic material or other components of the vectors used to carry the genetic material. Many times, side effects are only detectable after investigational products are tested in larger scale, pivotal clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. FDA guidance advises that patients treated with gene therapies undergo long-term follow-up observation for potential adverse events for as long as 15 years. If additional clinical or long-term follow-up experience indicates that any of our product candidates have side effects or cause serious or life-threatening side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked or limited.

Gene therapy is still a relatively new approach to disease treatment and adverse side effects could develop. A safety concern for gene therapies using lentiviral vectors has been the possibility of insertional oncogenesis, leading to malignant transformation of transduced cells and cellular outgrowth. As more patients are dosed with HSC gene therapies, it is expected that very rare cases of insertional oncogenesis may occur. For example, several patients with cerebral adrenoleukodystrophy treated in a third-party lentiviral gene therapy clinical trial have been diagnosed with treatment-related myelodysplastic syndrome to date. In addition, persistent clonal dominance due to vector integration has been observed in third-party HSC gene therapy clinical trials. While our HSC gene therapy approach is designed to avoid insertional oncogenesis, there can be no assurance that patients will not experience such adverse effects, including death. In addition, although in the future we may potentially implement molecular cytogenetic screening, there can be no assurance that we will successfully implement such screening procedures in a timely manner or at all, or that, if implemented, they will enhance the safety profile of our gene therapy product candidates. If any of our gene therapy product candidates demonstrates adverse side effects at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

In addition to side effects caused by our product candidates, the conditioning, administration process or related procedures, which we evaluate from time to time as part of our process improvement and optimization efforts, also can cause adverse side effects. A gene therapy patient is generally administered one or more myeloablative drugs to remove stem cells from the bone marrow to create sufficient space in the bone marrow for the modified gene-corrected stem cells to engraft and produce their progeny. This procedure causes side effects and, among other potential risks, can transiently compromise the patient's immune system, known as neutropenia, and reduce blood clotting, known as thrombocytopenia.

In 2019, we began transitioning, in connection with our Company-sponsored clinical trials, towards a new conditioning regimen for our product candidates utilizing busulfan as the myeloablative conditioning agent instead of the melphalan that we previously used. The use of this conditioning regimen is designed to utilize a precision dosing program, called TCI, to achieve a balance between the removal of a sufficient amount of bone marrow cells from a patient to aid engraftment of our genetically modified cells against potential risks, such as toxicity or graft failure. In addition, we are evaluating the potential future use of alternative conditioning agents in lieu of the current busulfan TCI conditioning regimen. For example, we have entered into a collaboration agreement with Jasper Therapeutics, Inc. and are currently evaluating the potential use of their respective monoclonal antibody conditioning agents. We are also evaluating the potential use of additional agents to tailor the conditioning regimen for certain disease indications. However, there can be no assurances these alternative conditioning regimens will be implemented or would be successful if implemented. Our conditioning regimens may not be successful or may nevertheless result in adverse side effects. For example, busulfan, the myeloablative agent currently used in our conditioning regimen, has been known to carry certain safety risks, including the risk of impairment to fertility in both men and women, and such impairment has been reported in some patients in our clinical trials. Moreover, in each of our ongoing clinical trials several adverse events, including suppression of neutrophils and platelet counts following the conditioning process, have been observed. While such adverse events in connection with conditioning are expected, if in the future any such adverse events caused by the conditioning process or related procedures continue at unexpected rates or degrees of severity, the FDA or other foreign regulatory authorities could order us to cease development of, or deny approval of, our product candidates for any or all targeted indications. There have been cases of therapy-related myelodysplastic syndrome, a type of blood disorder that is a potential precursor to acute myeloid leukemia, in patients with preexisting cancer where busulfan treatment was posited to be a contributing factor to this secondary malignancy. Although in the future we may potentially implement molecular cytogenetic screening as an additional risk reduction measure, there can be no guarantees that these procedures will be implemented in a timely manner or would be successful if implemented. Even if we are able to demonstrate that adverse events are not product-related, such occurrences could adversely affect patient recruitment or the ability of enrolled patients to complete the clinical trial, and lead to a decline in our stock price.

Additionally, if any of our product candidates receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or 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, a communication plan to health care practitioners, and restrictions on how or where the product can be distributed, dispensed or used. Furthermore, if we or others later identify undesirable side effects caused by our product candidates, several potentially significant negative consequences could result, including:

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

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates, lead to a decline in our stock price, and significantly harm our business, prospects, financial condition and results of operations.

We have never completed a pivotal or registrational clinical trial, and may be unable to do so for any product candidates we may develop.

We are at an early stage of development for all of our product candidates. As of the date of this Annual Report, only 24 patients have been dosed in our clinical trials, which includes 14 patients from our Fabry program that we deprioritized in January 2022. Our ongoing clinical trials, as well as potentially additional pivotal clinical trials (also referred to as registrational trials), must be completed in order to obtain FDA or other regulatory approval to market these product

candidates. We have limited experience in preparing, submitting and prosecuting regulatory filings, and have not previously submitted a biologics license application, or BLA, for any product candidate. Carrying out later-stage clinical trials is a complicated and lengthy process, and we do not expect that all data from patients participating in the clinical trials will be relevant or meaningful.

In addition, across our Company-sponsored clinical trials we have dosed only three patients in the United States, and our interactions with the FDA have generally been limited. We cannot be certain how many additional clinical trials of AVR-RD-02, AVR-RD-04 or any other product candidates will be required or how such trials should be designed. In order to commence a clinical trial in the United States, we are required to seek FDA acceptance of an IND for each of our product candidates. We cannot be sure any IND we submit to the FDA, or any similar CTA we submit in other countries, will be accepted. While we have received clearance from the FDA to commence clinical testing in the United States for our Company-sponsored Phase 1/2 clinical trial of AVR-RD-02 for Gaucher disease type 1 and the sponsor of the collaborator-led Phase 1/2 clinical trial for AVR-RD-04 for cystinosis has received the same, there can be no assurance that we will be able to submit and secure similar clearances for any of our other product candidates. We may also be required to conduct additional preclinical testing prior to filing an IND for any of our product candidates, and the results of any such testing may not be positive. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to a BLA submission and approval of any of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing any of our product candidates.

The ongoing Phase 1/2 clinical trial of AVR-RD-04 is being conducted by our collaborators at the University of California, San Diego. In addition, the planned Phase 1/2 clinical trial of AVR-RD-05 will be a collaborator-sponsored trial conducted by our collaborators at The University of Manchester; and the MHRA recently accepted its CTA application for this Phase 1/2 clinical trial. We do not control the design or administration of collaborator-sponsored trials, nor the submission or clearance of any IND or foreign equivalent required to conduct these trials, and the collaborator-sponsored trials could, depending on the actions of such third parties, jeopardize the validity of the clinical data generated, identify significant concerns with respect to our product candidates that could impact our findings or clinical trials, and adversely affect our ability to obtain marketing approval from the FDA or other applicable regulatory authorities. To the extent the results of these or other non-Company-sponsored trials are inconsistent with, or different from, the results of our planned Company-sponsored trials or raise concerns regarding our product candidates, the FDA or a foreign regulatory authority may question the results of the Company-sponsored trial, or subject such results to greater scrutiny than it otherwise would. In these circumstances, the FDA or such foreign regulatory authorities may require us to obtain and submit additional clinical data, which could delay clinical development or marketing approval of our product candidates. In addition, while collaborator-sponsored trials could be useful to inform our own clinical development efforts, there is no guarantee that we will be able to use the data from these trials to form the basis for regulatory authorization to conduct further clinical studies, or for regulatory approval of our product candidates. For example, regulators may require us to submit comparability or bridging studies to allow data generated in non-Company-sponsored studies to support the regulatory applications for or approvals of our product candidates, and we cannot be certain that such comparability or bridging studies, if any, would be successful or feasible.

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

Results from preclinical studies or early clinical trials are not necessarily predictive of future clinical trial results and are not necessarily indicative of final results. There can be no assurance that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials will be replicated or will continue in ongoing or future studies or trials. Furthermore, preliminary results may not be indicative of the final results of a trial after all data have been collected and analyzed. For example, in January 2022 we announced the deprioritization of our Fabry program due to several factors, including new clinical data showing variable engraftment patterns from the five most recently dosed Phase 2 FAB-GT patients. Although previously reported data from 13 patients treated across our clinical-stage programs had shown durable engraftment out 9 to 54 months, the new data from the five most recently dosed Phase 2 FAB-GT patients were discordant with these other data and showed variable engraftment. Data from three of the five patients showed both a reduction to near baseline levels in alpha-galactosidase A enzyme activity in leukocytes and plasma, and a reduction in vector copy number in whole blood, potentially suggesting resistance to persistent engraftment of the genetically modified cells observed at three to nine months post infusion of AVR-RD-01. Based on our internal assessment, we believe, due to the large degree of heterogeneity in Fabry disease, that in some cases there may be intrinsic resistance to engraftment related to the unique underlying pathophysiology of untreated Fabry disease, potentially caused by the persistently stressed vascular endothelium. However, while this belief is based on a thorough review and analysis conducted by the Company, it remains a

hypothesis and there can be no assurances that similar engraftment or other issues will not occur in clinical trials of our other product candidates, which are all based on our technology and the same HSC approach utilized for AVR-RD-01. For example, although we believe the variable engraftment data were caused by factors intrinsic to certain Fabry disease patients and we do not anticipate readthrough to other clinical trials, if the variable engraftment data were actually caused, directly or indirectly, by any other factors, including any aspect of our plato platform or the conditioning process, we could see similar issues in other clinical trials.

There is a high failure rate for gene therapy and biologic product candidates proceeding through clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, the design of a pivotal clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. Our Company has limited experience in designing and conducting clinical trials and we may be unable to design and execute a clinical trial to support regulatory approval.

We also may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy or the approval of competitive therapies during the period of our product candidate development. Any of our current or future product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies. Any such failure would cause us to abandon the product candidate.

Additionally, the clinical trials performed to date have been open-label studies and have been conducted at a limited number of clinical sites on a limited number of patients. An “open-label” clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment. Open-label clinical trials may be subject to a “patient bias” where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. Moreover, patients selected for early clinical studies often include the most severe sufferers and their symptoms may have been bound to improve notwithstanding the new treatment. In addition, open-label clinical trials may be subject to an “investigator bias” where those assessing and reviewing the physiological outcomes of the clinical trials are aware that patients have received treatment and may interpret the information more favorably given this knowledge. Because our clinical trials are ongoing, the data that we report are preliminary and subject to change. As is typical in open-label studies in which interim reports are provided, the safety and efficacy data are regularly reviewed and validated. As a result, certain data may change over time, including reductions or increases in the number of reported safety events, as well as the characterization of the severity or relatedness of safety events, until the database is locked at the end of the study.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

The timing and success of our patient enrollment and clinical trial activities depend on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting studies and obtaining regulatory approval of our product candidates may be delayed, including as a result of the ongoing COVID-19 pandemic, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether. For example, as a result of the COVID-19 pandemic, patient enrollment and dosing was temporarily paused in our ongoing clinical trials and certain data collection has been delayed. While patient enrollment and dosing activities have resumed, there could be additional pauses in the future as a result of the ongoing COVID-19 pandemic or other factors.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical trials in a timely manner or at all. Although we currently expect to have enrolled up to a total of ten patients by the end of 2023 in our Company-sponsored clinical trial of AVR-RD-02 for Gaucher disease type 1, which we refer to as the Guard1 clinical trial, there can be no assurances we will achieve that goal or any of our other patient enrollment goals.

Patient enrollment and trial completion is affected by factors including the:

- ability to enroll patients and conduct studies as a result of the ongoing COVID-19 pandemic;
- size of the patient population and process for identifying patients;
- design of the trial protocol;
- eligibility and exclusion criteria;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases, including any required pretreatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective patients;
- ability to obtain and maintain subject consent;
- risk that enrolled patients will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

We have expanded our patient enrollment activities to include patients who reside in a country other than the country where the applicable clinical site is located, and who are required to travel for some or all of the clinical testing and procedures required for patients in the applicable clinical trial. We have encountered and in the future may continue to encounter logistical and regulatory challenges that could delay or prevent any such international patients from successfully enrolling and completing clinical trial procedures, including delays in processing or obtaining patient travel visas or denials of entry at borders, potential travel disruptions, or de-prioritization or unavailability of resources at clinical sites for non-resident international clinical trial participants, any of which could delay our progress and completion of planned clinical trials and which would have an adverse effect on our business. In addition, once these international patients return to their home country they may need to travel back to the country where the applicable clinical site is located. If these patients are unwilling or unable to return to the clinical site for testing and procedures, progress and completion of the clinical trial could be delayed or prevented.

Our current product candidates are being developed to treat rare conditions. We plan to seek initial marketing approvals in the United States, Europe and certain other major markets, including Japan. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by FDA or other foreign regulatory authorities. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, clinical study sites and physicians;
- different standards for the conduct of clinical trials;
- the absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical studies can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays as a result of the ongoing COVID-19 pandemic;
- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical study sites;
- delays in obtaining required IRB approval at each clinical study site;
- delays in recruiting suitable patients to participate in our clinical studies;
- imposition of a clinical hold by regulatory agencies, after an inspection of our clinical study operations or study sites;
- failure by our CROs, other third parties or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical study sites or patients dropping out of a study;
- the occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues. In addition, if we make changes to our product candidates, or if collaborator-sponsored trials utilize different materials or manufacturing processes from ours to generate data, we may need to conduct additional studies to compare or bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. For example, we have transitioned our lentiviral vectors

to an LV2 version in connection with our plato platform implementation. In addition, the transition from LV1 to LV2 has required (and is anticipated to continue to require) submission of relevant data to the applicable regulatory authorities in connection with certain of our regulatory filings, including our INDs and CTAs, to demonstrate analytic comparability between LV1 and LV2. Our CTA (including amendments) and IND for our Guard1 clinical study of AVR-RD-02 for Gaucher disease type 1 in Canada and the United States, for which Health Canada has issued no objection letters and the FDA has cleared, respectively, included data utilizing LV2 and our automated manufacturing platform. While these applications included data relating to our LV2 lentiviral vector and our automated manufacturing process, which are elements of our plato platform, we expect that the FDA, Health Canada or other regulatory authorities will require us to undertake additional actions in connection with our transition to our plato platform, including submission of additional comparability studies in connection with future regulatory filings, which may result in delays, suspension or termination of ongoing or future clinical trials, or our inability to conduct our trials according to the plans or the timelines that we have envisioned. For example, the Phase 1/2 collaborator-sponsored clinical study of AVR-RD-04 for cystinosis in the United States, which has been cleared by the FDA, does not include our LV2 lentiviral vector or our automated manufacturing platform. Additionally, the study drug for the planned collaborator-sponsored clinical study of AVR-RD-05 for Hunter syndrome will not be manufactured using our plato platform, and neither the automated, closed manufacturing system nor LV2 will be used in connection with this clinical trial. Moreover, we are currently evaluating the implementation of an additional, new conditioning regimen that utilizes conditioning agents other than busulfan. We anticipate that we will be required to submit comparability data in future regulatory filings relating to our transition to LV2, the automated manufacturing platform and any new conditioning regimen that we implement. Any such filings may result in delay, suspension or termination of ongoing or future clinical trials pending our submission, and the applicable regulatory agency's review, of such updates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, 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 and results of operations.

If the results of our clinical studies are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling or a REMS that includes significant use or distribution restrictions or safety warnings;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical studies to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

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

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 studies, 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 studies 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 studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. If we are unable to obtain necessary regulatory approvals or labeling claims, our business, prospects, financial condition and results of operations would be materially and adversely affected.

Only one of our ongoing clinical trials utilizes our commercially-scalable plato platform.

While we have submitted and intend to continue to submit comparability studies to the FDA and other regulatory agencies, as needed, with respect to our implementation of our scalable plato platform, there can be no assurance that the FDA or other regulatory agencies will not in the future require us to conduct additional preclinical studies or clinical trials that could result in delays and additional costs in our development or commercialization programs for our product candidates, which could adversely affect our business. We intend to continue implementing our scalable plato platform, including heightened vector efficiency, our closed, automated manufacturing system and utilization of a customized conditioning regimen, in connection with each of our investigational product candidates. We have developed the plato platform to form the backbone of our commercial programs, with the intent of replacing our original academic platforms with improved solutions for delivering our gene therapy candidates to patients in multiple disease indications. We believe improvements to our plato platform may lead to better patient outcomes with our gene therapy candidates. In order to implement this transition, we have been and will be required to conduct additional studies to bridge our modified product candidates to earlier versions, including earlier versions utilized in collaborator-sponsored clinical studies, which could delay our clinical development plans or marketing approvals, if any. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, 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 and results of operations.

We face significant competition in our industry and there can be no assurance that our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.

We operate in a highly competitive segment of the biopharmaceutical market. We face competition from many different sources, including larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies, some of which are being marketed by large and international companies. In addition, we expect to compete with new treatments that are under development or may be advanced into the clinic by our competitors. There are a variety of product candidates, including gene therapies, in development for the indications that we are targeting.

We anticipate competing with biotechnology and pharmaceutical companies , many of which may have significantly greater resources than we do. For example, for Gaucher disease, Sanofi, Pfizer, and Takeda market existing enzyme replacement therapies, or ERTs, that represent the standard of care for Gaucher patients. For Gaucher disease we also expect to compete with oral therapies marketed by Johnson & Johnson and Sanofi. Sanofi also markets an enzyme replacement therapy for Pompe disease, and Takeda markets an enzyme replacement therapy for Hunter syndrome. Denali Therapeutics has an ERT in late-stage clinical development for Hunter syndrome. Cystinosis is currently treated by therapies marketed by Horizon Orphan, Mylan, Chiesi, Recordati, Orphan Europe and Leadiant Biosciences. In addition, we may compete with other gene therapy companies in our industry such as Freeline Therapeutics, Generation Bio, Eli Lilly and Company or Graphite Bio. Freeline Therapeutics, for example, is developing an adeno-associated virus, or AAV based gene therapy for Gaucher disease type 1. Moreover, a number of gene therapy companies have announced preclinical or clinical non-viral and adeno-associated viral based gene therapy programs that, if successful in obtaining regulatory approval, could compete with our gene therapies. For example, Gene Cradle has announced a pre-clinical program for infantile onset Pompe disease and late onset Pompe disease.

Many of our competitors have significantly greater financial, product candidate development, manufacturing and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for their products, and mergers and acquisitions within these industries may result in even more resources being concentrated among a smaller number of larger competitors. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries.

Our business would be materially and adversely affected if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, have broader market acceptance, are more convenient or are less expensive than any product candidate that we may develop.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

While we intend to seek designations for our product candidates with the FDA and comparable foreign regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.

The FDA and comparable foreign regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. However, there can be no assurance that we will successfully obtain such designations for any of our product candidates. In addition, while such designations could expedite the development or approval process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

We may seek a Breakthrough Therapy Designation for some of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

We may seek an accelerated approval pathway for one or more of our product candidates from the FDA or comparable foreign regulatory authorities. The FDA may grant accelerated approval to a therapeutic candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. If granted, accelerated approval is usually contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit, and the FDA is permitted to require, as appropriate, that such studies be underway prior to approval or within a specified period after the date of approval. Sponsors must also update FDA on the status of these studies, and under FDORA, the FDA has increased authority to withdraw approval of a drug granted accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit.

Prior to seeking accelerated approval, we will seek feedback from the FDA or comparable foreign regulatory authorities and will otherwise evaluate our ability to seek and receive such accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit a BLA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that after subsequent feedback from the FDA or comparable foreign regulatory authorities, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval, there can be no assurance that such application will be accepted or that any approval will be granted on a timely basis, or at all. The FDA, EMA or other comparable foreign regulatory

authorities could also require us to conduct further studies prior to considering our application or granting approval of any type, including, for example, if other products are approved via the accelerated pathway and subsequently converted by FDA to full approval. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidate would result in a longer time period to commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace. Moreover, even if we are able to obtain accelerated approval for any of our product candidates, there is no guarantee that post-approval studies will be able to confirm the clinical benefit, which could cause FDA to withdraw our approval.

We may also pursue programs or designations from foreign regulatory authorities, such as the UK's Innovative Licensing and Access Pathway, or ILAP, which aims to accelerate the time to market and facilitate patient access to certain types of medicinal products in development which target a life-threatening or seriously debilitating condition, or where there is a significant patient or public health need. The first step in the ILAP is receipt of an Innovation Passport, which allows for enhanced engagement with the MHRA and its partner agencies. In October 2022, we announced that the MHRA had granted an Innovation Passport to AVR-RD-02, which we are evaluating for the treatment of Gaucher disease. However, although the goal of ILAP and the Innovation Passport is to reduce the time to market and enable earlier patient access, receipt of this designation does not accelerate conduct of clinical trials or mean that the regulatory requirements are less stringent, nor does it ensure that any future application for marketing authorization will be approved or that any approval will be granted within a particular timeframe.

In addition, we may seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. In December 2021, we received Fast Track Designation from the FDA for AVR-RD-02 for the treatment of Gaucher disease, and in July 2021 we received Fast Track Designation from the FDA for AVR-RD-04 for the treatment of cystinosis to improve renal function. However, the FDA has broad discretion whether or not to grant Fast Track designation, so even if we believe another product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA approval. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

In addition, we may seek a regenerative medicine advanced therapy, or RMAT, designation for some of our product candidates. 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. Gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. The RMAT program is intended to facilitate efficient development and expedite review of RMATs, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition. A new drug application or a BLA for an RMAT may be eligible for priority review or accelerated approval through (1) surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit or (2) reliance upon data obtained from a meaningful number of sites. Benefits of such designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. RMAT designation is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a regenerative medicine advanced therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of RMAT designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify for RMAT designation, the FDA may later decide that the biological products no longer meet the conditions for qualification.

We may be unable to obtain orphan drug designation for our product candidates and, even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or

condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products may designate a medicinal product as an orphan medicinal product if it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union. Additionally, orphan designation may be granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the product. In either case, the applicant must be able to establish that there is no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition.

In October 2019 and March 2020, the FDA granted our requests for orphan drug designation for AVR-RD-02 for the treatment of Gaucher disease and AVR-RD-04 for the treatment of cystinosis, respectively. Additionally, in July 2022, we announced that the FDA granted our request for orphan drug designation for AVR-RD-05 for the treatment of Hunter syndrome. In September 2020 and March 2021 we announced that the European Commission granted our request for orphan drug designation for AVR-RD-02 for the treatment of Gaucher disease and AVR-RD-04 for the treatment of cystinosis, respectively. However, if we request orphan drug designation (or the foreign equivalent) for any other product candidates, there can be no assurances that the FDA or applicable foreign regulatory authorities will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not mean that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation 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 foreign regulatory authorities from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 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 or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency 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 patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition in the United States. Even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication at any time if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

We have received rare pediatric disease designation, or RPDD, for several of our product candidates. However, a marketing application for a product candidate with RPDD, if approved, may not meet the eligibility criteria for a Priority Review Voucher, or PRV, or the RPDD program may sunset before the FDA is able to consider us for a voucher.

We have received rare pediatric disease designation, or RPDD, for AVR-RD-02 for the treatment of Gaucher disease, AVR-RD-04 for the treatment of cystinosis, and AVR-RD-05 for the treatment of Hunter syndrome. Designation of a drug or

biologic as a product for a rare pediatric disease does not guarantee that a BLA for such drug or biologic will meet the eligibility criteria for a rare pediatric disease PRV at the time the application is approved. Under the Federal Food, Drug, and Cosmetic Act, we will need to request a rare pediatric disease PRV in our original BLA for AVR-RD-05. The FDA may determine that a BLA for AVR-RD-05, if approved, does not meet the eligibility criteria for a PRV, including for the following reasons:

- The disease indication no longer meets the definition of a rare pediatric disease;
- the BLA contains an active ingredient that has been previously approved in a BLA;
- the BLA is not deemed eligible for priority review;
- the BLA does not rely on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population (that is, if the BLA does not contain sufficient clinical data to allow for adequate labeling for use by the full range of affected pediatric patients); or
- the BLA is approved for a different adult indication than the rare pediatric disease for which the product candidate is designated.
- The authority for the FDA to award rare pediatric disease PRVs for drugs that have received rare pediatric disease designation prior to September 30, 2024 currently expires on September 30, 2026. If the BLA for any of our product candidates with RPDD is not approved prior to September 30, 2026 for any reason, regardless of whether it meets the criteria for a rare pediatric disease PRV, it will not be eligible for a PRV. However, it is also possible the authority for FDA to award rare pediatric disease PRVs will be further extended through federal lawmaking.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight.

Even if we obtain any regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with gene therapies undergo long-term follow-up observation for potential adverse events for as long as 15 years. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, requirements and adherence to commitments made in the BLA or foreign marketing application. Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements including ensuring that quality control and manufacturing procedures conform to cGMP regulations and applicable product tracking and tracing requirements. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

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

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;

- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; 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 adversely affect our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

Our focus on developing our current product candidates may not yield any commercially viable products, and our failure to successfully identify and develop additional product candidates could impair our ability to grow.

While we initially pursued a growth strategy to identify, develop and market additional product candidates, we are not currently actively seeking additional product candidates beyond our existing product candidates. We may spend several years completing our development of any particular product candidates, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential than our product candidates. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

Because our internal research capabilities are limited, we may be dependent upon biotechnology companies, academic scientists and other researchers to sell or license product candidates, approved products or the underlying technology to us. The success of this strategy depends partly upon our ability to identify, select, discover and acquire promising product candidates and products.

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as ERT. We have not yet succeeded and may never succeed in demonstrating efficacy and safety of our product candidates or any future product candidates in clinical trials or in obtaining marketing approval thereafter. Accordingly, our focus on treating these diseases may not result in the development of commercially viable products.

If we are unsuccessful in our development efforts, we may not be able to advance the development of our product candidates, commercialize products, raise capital, expand our business or continue our operations.

Risks related to manufacturing

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

The manufacturing process we use to produce our product candidates is complex, novel and has not been validated for commercial use. Several factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers.

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

In addition, the FDA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA or other foreign regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Even 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 or product recalls. There is no assurance we will not experience lot failures in the future. Lot failures or product recalls could cause us to delay clinical trials, or, if approved, commercial product launches, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects. Our manufacturing process relies on a platform structure, which we refer to as our plato platform, and, if we experience delays, deviations or failures that impact that platform, such delays, deviations or failures could have an adverse impact on our development products or future commercialization programs.

Risks related to our reliance on third parties

We expect to rely on third parties to conduct some or all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our vector production, product manufacturing, protocol development, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to these items. Any of these third parties may terminate their engagements with us or renegotiate the terms of our agreements at any time. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our preclinical and clinical studies are conducted in accordance with the study plan, protocols and regulatory requirements.

Even with relevant experience and expertise, our third-party manufacturers may encounter difficulties in production, such as initial production, managing the transition from early to late-stage clinical and commercial manufacturing, and ensuring that the product meets required specifications. These difficulties may include delays, failure or inability achieving production yields, establishing and maintaining stage-appropriate cGMP quality procedures, operator error, shortages of qualified personnel, and compliance with federal, state and foreign regulations. We cannot make any assurances that these difficulties will not occur in the future, or that we will be able to resolve or address them in a timely manner or at all as problems arise.

If our contract counterparties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the preclinical and clinical studies required to support approval of our product candidates or the FDA or other regulatory agencies may refuse to accept our clinical or preclinical data. For example, in 2019 we encountered delays in the enrollment of patients in the Company-sponsored Guard1 clinical trial of AVR-RD-02 for Gaucher disease. While a number of interested patients had been identified for the Guard1 clinical trial, we encountered patient pre-screening failures that impacted the commencement of enrollment in these studies. Additionally, as a result of the COVID-19 pandemic, in 2020 we encountered protracted timelines with our investigational site startup activities for our Guard1 clinical trial, which also impacted patient enrollment. In 2020, a kidney biopsy was conducted on the third patient in the FAB-GT clinical trial of AVR-RD-01, but due to human error in processing the biopsy sample at the external laboratory vendor, the kidney Gb3 inclusions could not be evaluated and anticipated data was not available.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the impact of the ongoing COVID-19 pandemic or the bankruptcy of the manufacturer or supplier.

Any of these events could lead to delays of our preclinical and clinical studies or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

We currently rely, and expect to continue to rely, on sole source suppliers for our automated, closed cell processing system; vector supply; plasmid supply; cell culture media supply; and drug product manufacturing. In addition, we are dependent on a limited number of suppliers for some of our other components and materials used in our product candidates.

We have moved our cell processing to an automated, closed system with a sole source supplier. In addition, we currently rely, and expect to continue to rely, on sole source suppliers for vector supply, plasmid supply and cell culture media, as well as drug product manufacturing for our Company-sponsored clinical trials. Our sole source suppliers may be unwilling or unable to supply product to us reliably, continuously or at the levels we anticipate or are required by our clinical trial activities. Such suppliers could still delay, suspend, or terminate supply of product to us for a number of reasons, including manufacturing or quality issues, payment disputes with us, intellectual property disputes with third parties, bankruptcy or insolvency, earthquakes or other natural disasters or other occurrences.

In addition, we currently depend on a limited number of suppliers for some of the other components necessary for our product candidates. We cannot be sure that any of our suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a sole source or limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components and equipment. Any of our 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 and materials could take a substantial amount of time and it may be difficult or impossible to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we are required to switch to a replacement supplier or manufacture materials ourselves, the manufacture and delivery of our product candidates could be interrupted for an extended period, adversely affecting our business. Establishing additional or replacement suppliers may not be accomplished quickly, and we may not be able to enter agreements with replacement suppliers on reasonable terms, if at all. In either scenario, our clinical trials supply could be delayed significantly as we establish alternative supply sources. In some cases, the technical skills required to manufacture our products or product

candidates may be unique or proprietary to the original CMO and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills to a back-up or alternate supplier, or we may be unable to transfer such skills at all. 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. For example, the FDA could require additional supplemental bridging data if we rely upon a new supplier. We may be unsuccessful in demonstrating the comparability of clinical supplies which could require the conduct of additional clinical trials. While we seek to maintain adequate inventory of the components and materials used in our product candidates, 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 conduct our clinical trials and, if our product candidates are approved, to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, the FDA must review and approve the individual components of our production process, which includes the manufacturing processes and facilities of our suppliers. Our current suppliers have not undergone this process, nor have they had any components included in any product approved by the FDA.

Our reliance on suppliers subjects us to a number of risks that could materially harm our reputation, business, and financial condition, including, among other things:

- delays in production, supply, shipment or delivery as a result of the ongoing COVID-19 pandemic or trade sanctions, embargoes, and heightened export requirements resulting from the war in Ukraine;
- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, our costs could significantly increase and our ability to conduct our clinical trials and, if our product candidates are approved, to meet demand for our products could be impacted.

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.

We currently rely on sole source suppliers of our automated, closed cell processing system; vector supply; plasmid supply; cell culture media; as well as drug product manufacturing for our Company-sponsored clinical trials. In addition, we currently depend on a limited number of suppliers for some of the other components necessary for our product candidates. Each of our suppliers may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical studies 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 clinical studies 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 BLA on a timely basis and must adhere to the FDA's good laboratory practices, or GLP, and cGMP regulations enforced by the FDA through its facilities inspection program. Some of our contract manufacturers have not produced a commercially-approved product and have never been inspected by the FDA before. 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, or if the FDA is unable to conduct such an inspection due to the ongoing COVID-19 pandemic, the FDA may issue a complete response letter or defer action on our applications, and approval of the products may be delayed or may 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 study 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 and results of operations may be materially harmed.

These factors could cause the delay of clinical studies, 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 preclinical and clinical studies may be delayed.

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 rely on third parties to manufacture our vectors and our product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy approach, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer 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, such as 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, 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 trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in

some cases we may share these rights with other parties. 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 in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to commercialization of our product candidates

If we are unable to establish sales, distribution and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we will be unable to generate any product revenue.

To successfully commercialize any of our product candidates, if approved, we will need to develop our commercial capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract sales force to market any product candidate we may develop will be expensive and time-consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may enter into collaborations regarding any approved product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded sales, distribution and marketing operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates, if approved. Without an internal team or the support of a third-party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for serious lysosomal disorders. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States and elsewhere may turn out to be lower than expected or may not be otherwise amenable to treatment with our products, patients may become increasingly difficult to identify and access, and any approval we receive from regulatory agencies may be for a narrower indication and smaller patient population than anticipated, all of which would adversely affect our business, financial condition, results of operations and prospects.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Even if we obtain any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party payors accepting gene therapy products in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments, including any similar generic treatments;
- the efficacy and safety as demonstrated in pivotal clinical trials and published in peer-reviewed journals;
- the prevalence and severity of any adverse events or side effects, including any limitations or warnings contained in a product's approved labeling or that are later found to be associated with a product, including in findings from long-term follow-up studies;
- the prevalence and severity of any side effects resulting from the conditioning regimen for the administration of our product candidates;
- the ability to offer the products for sale at competitive prices;

- the clinical indications for which the products are approved by the FDA or comparable regulatory agencies;
- the relative convenience and ease of dosing and 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 and timing of market introduction of competitive products;
- restrictions on how the product is distributed;
- the availability of accessible and skilled healthcare centers capable of administering our treatments;
- publicity concerning our products or competing products and treatments; and
- favorable third-party insurance coverage and sufficient reimbursement.

Sales of medical products also depend 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.

Even if a product candidate displays a favorable efficacy and safety profile in preclinical and clinical studies, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

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

We are currently conducting clinical trials for our product candidates in the United States, Canada and Australia, and plan to expand to other geographies. If any of our product candidates are approved for commercialization, we may enter into agreements with third parties to market them on a worldwide basis or in more limited geographical regions. We expect that we will be subject to additional risks related to entering into international business relationships, including:

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

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

The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. In the United States, recently enacted legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our or their commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval. See section entitled "*Business – Government Regulation – Coverage and Reimbursement*."

Our ability to successfully commercialize our product candidates or any other products that we or they may develop also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford treatments. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, if approved. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by CMS, an agency within the HHS as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow CMS to a substantial degree. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs and commercial payors are critical to new product acceptance. Government authorities and other third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and certain other major markets where we plan to commercialize may put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems, and pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Moreover, efforts by governmental and other third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing

pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

Our target patient populations are relatively small, as a result of which the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates, if approved. Moreover, if approved for marketing, because our product candidates are designed to provide their intended therapeutic benefit from a single administration, treatment with our product candidates may result in a decrease in the available pool of target patients.

Healthcare legislative reform measures and constraints on national budget social security systems may have a material adverse effect on our business and results of operations.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. There have been, and likely will continue to be, legislative and regulatory proposals at the federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. See Section entitled *"Business - Government Regulation – Healthcare Reform."*

The continuing efforts of the government, insurance companies, managed care organizations and other payers of healthcare services to contain or reduce costs of healthcare may adversely affect:

- the demand for any of our product candidates, if approved;
- the ability to set a price that we believe is fair for any of our product candidates, if approved;
- our ability to generate revenues and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

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

Moreover, increasing efforts by governmental and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. There has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs.

We expect that the healthcare reform measures that have been adopted and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. In August 2022, the Inflation Reduction Act of 2022, or the IRA, was signed into law. The IRA includes several provisions that will impact our business to varying degrees, including provisions that create a $2,000 out-of-pocket cap for Medicare Part D beneficiaries, impose new manufacturer financial

liability on all drugs in Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D pricing for certain high-cost drugs and biologics without generic or biosimilar competition, require companies to pay rebates to Medicare for drug prices that increase faster than inflation, and delay the rebate rule that would require pass through of pharmacy benefit manager rebates to beneficiaries. The effect of the IRA on our business and the healthcare industry in general is not yet known. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates.

Inadequate funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA and other government employees and stop critical activities. Since March 2020, when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume pre-pandemic levels of inspection activities, including routine surveillance, bioresearch monitoring and pre-approval inspections. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic or any other public health crisis and may experience delays in their regulatory activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future shutdowns of other government agencies, such as the SEC, may also impact our business through review of our public filings and our ability to access the public markets.

Any contamination in our manufacturing process, shortages of materials or failure of any of our key suppliers to deliver necessary components could result in interruption in the supply of our product candidates and delays in our clinical development or commercialization schedules.

Given the nature of biologics manufacturing, there is a risk of contamination in our manufacturing processes. Any contamination could materially adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage.

Some of the materials required in our manufacturing process are derived from biologic sources. Such 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 our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially and adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Risks related to our business operations

Our gene therapy approach utilizes lentiviral vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology, with only a limited number of gene therapy products approved to date. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of

the public or the medical community. In particular, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with 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 we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia, myelodysplastic syndromes and deaths seen in other trials using other vectors. Adverse events in our clinical studies or discovered in long-term follow-up, even if not ultimately attributable to our product candidates (such as the many adverse events that typically arise from the conditioning process), or adverse events in other gene therapy trials, and the resulting publicity could result in a decline in our stock price, increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

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

We are highly dependent on principal members of our executive team and key employees, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time, as all of our employees are "at will" employees. We do not maintain "key person" insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current executive or key employees might impede the achievement of our research, development and commercialization objectives. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. We implemented a reduction in force in January 2022 in connection with the deprioritization of our Fabry disease program, and through the first half of 2022 we continued to streamline employee headcount including senior management. Reductions in force, management changes and program reprioritizations can have an adverse impact on employee morale. While we believe our relations with our continuing employees to be good, there can be no assurance that we can avoid hiring and retention challenges for skilled personnel in the future. There is currently a shortage of skilled executives and other personnel in our industry, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, our ability to recruit and retain qualified personnel could be impacted by other factors, such as remote or hybrid working arrangements, including those resulting from the ongoing COVID-19 pandemic, which could impact employees' productivity and morale, as well as any failure to succeed in preclinical or clinical trials. In addition, in recent months, the market price of our common stock has experienced significant downward pressure, resulting in "underwater" or "out-of-the-money" stock options for many of our employees, thereby limiting the desired retentive effect that our equity incentive program was intended to achieve. The inability to recruit or the loss of the services of any executive, key employee, skilled personnel, consultant or advisor may impede the progress of our research, development and commercialization objectives.

We may need to expand or streamline our operations and we may experience difficulties in managing any such changes, which could disrupt our operations.

As we mature, we may need to rapidly expand our full-time employee base and to hire more consultants and contractors. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

Conversely, headwinds in the overall economy and limited availability of suitable financing to meet our needs could constrain our ability to achieve our growth objectives, and could in turn lead to reductions in force or scaling back of business operations, that could impact employee morale and adversely impact our ability to manage ongoing operations.

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and, in the longer term, build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

We may not be successful in identifying and pursuing any strategic opportunities for our programs, our technology or our plato platform, and any strategic transactions that we may consummate in the future could have negative consequences.

In addition to our research and development efforts for our pipeline candidates, as part of our business strategy, from time to time, we evaluate and intend to continue to evaluate opportunities to collaborate, partner, enter into joint ventures or undertake other strategic initiatives with third parties with respect to one or more of our programs, our technology or our plato platform. However, there can be no assurance that we will be able to successfully consummate any particular strategic transaction. These efforts may be costly, time-consuming and complex and we may incur significant legal, accounting and advisory fees and other expenses, some of which may be incurred regardless of whether we successfully enter into a transaction.

Furthermore, any strategic transactions that we may pursue could have a variety of negative consequences and we may enter into a transaction that yields unexpected results that adversely affects our business and decreases the remaining cash available for use in our business. There can be no assurances that any particular course of action, business arrangement or transaction, or series of transactions, will be pursued, successfully consummated, lead to increased stockholder value, or achieve the anticipated results.

We may not realize any additional value in a strategic transaction.

The market capitalization of our company is below the value of our cash and cash equivalents. Potential counterparties in a strategic transaction involving our company may place minimal or no value on our assets, including the programs in our pipeline. Further, the development and any potential commercialization of our product candidates will require substantial additional cash to fund the costs associated with conducting the necessary preclinical and clinical testing and obtaining regulatory approval. Consequently, any potential counterparty in a strategic transaction involving our company may choose not to spend additional resources and continue development of our product candidates and may attribute little or no value, in such a transaction, to those product candidates.

Our ability to pursue strategic transactions depends on our ability to retain our employees.

Our ability to pursue strategic transactions depends upon our ability to retain our employees, the loss of whose services may adversely impact the ability to identify, negotiate and consummate such transaction. In January 2022, we restructured our organization, which significantly reduced our workforce in order to conserve our capital resources. Our cash conservation activities may yield unintended consequences, such as attrition beyond our planned reduction in workforce and reduced employee morale, which may cause remaining employees to seek alternative employment. If we are unable to successfully retain our remaining personnel, we are at risk of a disruption to our exploration and consummation of one or more strategic transactions as well as business operations.

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, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA or of other foreign regulatory authorities, provide accurate information to the FDA and other foreign 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 conduct in

the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of healthcare professional interactions, drug pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations. We can face serious consequences for violations.

Among other matters, U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations, which are collectively referred to as Trade Laws, prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase in time. We plan to engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations, and other regulatory approvals and we can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities. The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the United States Foreign Corrupt Practices Act's accounting provisions.

We are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws health information privacy and security laws, and other health care laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

We are subject, and may be increasingly subject if we obtain FDA approval for any of our product candidates , to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. See Section entitled "Business - Government Regulation - Other Healthcare Laws and Compliance Requirements."

These laws will impact, among other things, our clinical trial programs, healthcare professional interactions, grant making activities, and our anticipated sales, marketing and medical educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert a company's attention from the business.

The failure to comply with any of these laws or regulatory requirements subjects entities to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in significant civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion from participation in federal and state funded healthcare programs (such as Medicare and Medicaid), contractual damages and the curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, that person or entity may

be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Prohibitions or restrictions on personnel, sales or withdrawal of future marketed products could materially affect business in an adverse way.

Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Failure to comply with health and data protection laws and regulations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business.

We and any potential collaborators may be subject to federal, state, and foreign data protection laws and regulations (i.e., laws and regulations that address privacy and data security). In the United States, numerous federal and state laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA, as amended by HITECH. Depending on the facts and circumstances, we could be subject to civil, criminal, and administrative penalties if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

Compliance with U.S. and international data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. Failure to comply with these laws and regulations could result in government enforcement actions (which could include civil, criminal and administrative penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial patients, employees and other individuals about whom we or our potential collaborators obtain personal information, as well as the providers who share this information with us, may limit our ability to collect, use and disclose the information. Claims that we have violated individuals' privacy rights, failed to comply with data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time-consuming to defend and could result in adverse publicity that could harm our business.

European data collection is governed by restrictive regulations governing the use, processing and cross-border transfer of personal information.

We currently plan to conduct clinical trials in the European Union, or EU, and the United Kingdom, or UK, and as a result will be subject to additional privacy restrictions. The collection, use, disclosure, transfer or other processing of personal health data in the EU and the UK is governed by the provisions of the GDPR (references to the GDPR include the "UK GDPR" unless specified otherwise). 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, providing information to individuals regarding data processing activities, obtaining consent from individuals to whom the data processing relates, responding to additional data subject requests, imposing notification of personal data breaches to the competent national data protection authorities, implementing safeguards in connection with the security and confidentiality of the personal data, accountability requirements and taking certain measures when engaging third-party processors. The GDPR informs our obligations with respect to any clinical trials conducted in the EU or the UK. Its definition of personal data includes coded data, requires changes to informed consent practices and detailed notices for clinical trial subjects and investigators. In addition, the GDPR imposes strict rules on the transfer of personal data out of the EU or the UK, including to the United States (see below). The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal data and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros (£ 17.5 million), whichever is greater, and 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 EU member states or the UK may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric, or health data.

Given the breadth and depth of its obligations, complying with the GDPR's requirements is rigorous and time intensive and requires significant resources and assessment 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 EU.

It is possible that over time the GDPR and the UK GDPR will diverge further. The UK government has announced plans to reform the data protection legal framework in the UK in its Data Reform Bill but this is not yet in final form. This lack of clarity on future UK laws and regulations and their interaction with EU laws and regulations could add legal risk, uncertainty, complexity and cost to our handling of personal information and our privacy and data security compliance programs and could require us to implement different compliance measures for the UK and the EU.

To enable the transfer of personal data outside of the EU or the UK, adequate safeguards must be implemented in compliance with the GDPR laws. On June 4, 2021, the EC issued new forms of standard contractual clauses for data transfers from controllers or processors in the EU (or otherwise subject to the GDPR) to controllers or processors established outside the EU (and not subject to the GDPR). As of December 27, 2022 the new standard contractual clauses replace the standard contractual clauses that were adopted previously under the EU Data Protection Directive. The UK is not subject to the EC's new standard contractual clauses but has published the UK International Data Transfer Agreement and the International Data Transfer Addendum to the new standard contractual clauses (the "IDTA"), which enable transfers from the UK. For new transfers, the IDTA already needs to be in place, and it must be in place for all existing transfers from the UK from March 21, 2024. Companies relying on standard contractual clauses of IDTA to govern transfers of personal data to third countries (in particular the United States) will also need to assess whether the data importer can ensure sufficient guarantees for safeguarding the personal data under GDPR, including an analysis of the laws in the recipient's country. We are required to implement these new safeguards when conducting restricted data transfers under the EU and UK GDPR and doing so will require significant effort and cost.

We have yet to adopt and implement comprehensive processes, systems and other relevant measures within our organization, and/or with our relevant collaborators, service providers, contractors or consultants, which are appropriate to address relevant requirements relating to international transfers of personal data from Europe, and to minimize the potential impacts and risks resulting from those requirements, across our organization. Failure to implement valid mechanisms for personal data transfers from Europe may result in our facing increased exposure to regulatory actions, substantial fines and injunctions against processing personal data from Europe. Inability to export personal data may also: restrict our activities outside Europe; limit our ability to collaborate with partners as well as other service providers, contractors and other companies outside of Europe; and/or require us to increase our processing capabilities within Europe at significant expense or otherwise cause us to change the geographical location or segregation of our relevant systems and operations – any or all of which could adversely affect our operations or financial results. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of delivering our services and operating our business. The type of challenges we face in Europe will likely also arise in other jurisdictions that adopt laws similar in construction to the GDPR or regulatory frameworks of equivalent complexity.

Although the UK is regarded as a third country under the EU GDPR, the EC has issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the EU to the UK remain unrestricted. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not

regarded by the UK as providing adequate protection. The UK government has confirmed that personal data transfers from the UK to the EU remain free flowing.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates including in clinical studies and the future sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- the impairment of our business reputation;
- the withdrawal of clinical study participants;
- costs due to related litigation;
- the distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry master product liability insurance of $5.0 million per occurrence and $5.0 million in the aggregate in the United States. For studies conducted in certain countries outside the United States, we maintain local admitted policies with varying limits. We believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by certain of our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life- threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

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

could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2022 and 2021, we had federal and state net operating loss carryforwards of $340.4 million and $313.0 million, respectively, and federal research and development tax credit carryforwards of approximately $6.8 million and $6.2 million, respectively. If not utilized, the net operating loss carryforwards and research and development credits will generally expire at various dates through 2038 (other than federal net operating loss carryforwards generated in taxable years beginning after December 31, 2017, which are not subject to expiration and generally may not be carried back to prior taxable years except that net operating losses generated in 2018, 2019 and 2020 may be carried back five taxable years). These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percentage point change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We may have experienced ownership changes in the past. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurred or occurs and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations. For taxable years beginning after December 31, 2020, deductions for federal net operating losses arising in taxable years beginning after December 31, 2017 may only offset 80% of taxable income.

Risks related to our intellectual property

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and *inter partes* reexamination proceedings before the U.S. Patent and Trademark Office, or USPTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we or our licensors are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. In particular, we are aware of issued patents in the United States that cover the lentiviral vectors used in the manufacture of our product candidates. While we believe that we have reasonable defenses against a claim of infringement, potentially including that certain of these patents are expected to expire prior to commercializing our product candidates, if approved, in the United States, there can be no assurance that we will prevail in any such action by the holder of these patents. In the event that the holder of these patents seeks to enforce its patent rights and our defenses against a claim of infringement are unsuccessful, we may not be able to commercialize our product candidates in the United States, if approved, without first obtaining a license to some or all of

these patents, which may not be available on commercially reasonable terms or at all. In addition, the defense of any claim of infringement, even if successful, is time-consuming, expensive and diverts the attention of our management from our ongoing business operations.

Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe or be alleged to infringe. In addition, third parties may obtain patents in the future and claim that use of our or our licensors' technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. Even in the absence of a finding of infringement, we may choose to obtain a license, if such a license is available. A successful claim of patent or other intellectual property infringement against us could materially adversely affect our business, results of operations and financial condition.

Our rights to develop and commercialize our product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.

We depend upon the intellectual property rights granted to us under licenses from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our gene therapy product candidates. In particular, we have in-licensed certain intellectual property rights and know-how from the University Health Network (relevant to AVR-RD-01 and our Fabry program, which we deprioritized in January 2022) and affiliates of Lund University (relevant to AVR-RD-02 and our Gaucher type 1 and type 3 programs). In addition, we have in-licensed patents and patent applications from BioMarin Pharmaceutical Inc., or BioMarin (relevant to AVR-RD-03 and our Pompe program), GenStem Therapeutics, Inc., which was subsequently assigned to Papillon (relevant to AVR-RD-04 and our cystinosis program) and The University of Manchester (relevant to AVR-RD-05 and our Hunter program), directed to compositions and methods related to the manufacture and use of AVR-RD-03, AVR-RD-04 and AVR-RD-05, respectively. Any termination of these licenses could result in the loss of significant rights and could harm or prevent our ability to commercialize our product candidates.

Each of our existing licenses are exclusive but are limited to particular fields, such as Fabry disease, cystinosis, Gaucher disease type 1, Hunter syndrome, or Pompe disease, and are subject to certain retained rights. Absent an amendment or additional agreement, we may not have the right to use intellectual property in-licensed for one of our programs for another program. In addition, licenses that we may enter into in the future may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses. Licenses to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business and financial condition.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. For example, pursuant to each of our intellectual property licenses with Papillon, BioMarin, the rights holders associated with Lund University, and The University of Manchester, our licensors retain control of such activities. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected.

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected product candidates.

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

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on manufacturing and other know-how, patents, trade secrets, trademarks, license agreements and contractual provisions to establish our intellectual property rights and protect our products. These legal means, however, afford only limited protection and may not adequately protect our rights. The failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties to make competing products or impact our ability to develop, manufacture and market our products, if approved, on a commercially viable basis, or at all, which could have a material adverse effect on our financial condition and results of operations.

In particular, we rely primarily on trade secrets, know-how and other unpatented technology, which are difficult to protect. Although we seek such protection in part by entering into confidentiality agreements with our vendors, employees, consultants and others who may have access to proprietary information, we cannot be certain that these agreements will not be breached, adequate remedies for any breach would be available or our trade secrets, know-how and other unpatented proprietary technology will not otherwise become known to or be independently developed by our competitors. If we are unsuccessful in protecting our intellectual property rights, sales of our products may suffer and our ability to generate revenue could be severely impacted.

Our licensors and we have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States related to current and future product candidates that are important to our business. However, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents, whether the claims of any issued patents will provide us with a competitive advantage, or whether we will be able to successfully pursue patent applications in the future related to our current or future product candidates. While we have in-licensed patents and patent applications relevant to AVR-RD-03 and AVR-RD-05, we currently have no owned or in-licensed patents or patent applications covering AVR-RD-01, or AVR-RD-02, and the patent applications that we in-licensed related to AVR-RD-04 are at a very early stage. Many of our product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all.

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

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. Although our license agreements grant us worldwide rights, and our currently in-licensed U.S. patent rights have certain corresponding foreign patents or patent applications, there can be no assurance that we will obtain or maintain such corresponding patents or patent applications with respect to any future license agreements. 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 even in jurisdictions where we and our licensors pursue patent protection. Consequently, we and our licensors may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we and our licensors pursue patent protection, 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 pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

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

If one of our licensing partners or we initiate legal proceedings against a third-party to enforce a patent covering one of our product candidates, should such a patent issue, the defendant could counterclaim that the patent covering our product candidate 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, 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, post grant review, *inter partes* review and equivalent 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. 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. Such a loss of patent protection could have a material adverse impact on our business.

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 and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have 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. While we have confidence in these individuals, organizations and systems, agreements or 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 by competitors.

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.

Certain 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 personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. Our licensors may face similar risks, which could have an adverse impact on intellectual property that is licensed to us.

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

We may be subject to claims challenging the inventorship or ownership of the patents and other intellectual property that we own or license.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own; our licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

Some intellectual property which we have in-licensed may have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements, and a preference for U.S. industry. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.

Some of the intellectual property rights we have licensed, including rights licensed to us by Papillon, may have been generated through the use of U.S. government and California state funding and may therefore be subject to certain federal and state laws and regulations. For example, with respect to the AVR-RD-04 program for cystinosis, the NIH previously granted funding to UCSD for certain research in connection with the development of UCSD's gene therapy program for cystinosis, which we originally licensed from GenStem Therapeutics, Inc., who subsequently assigned the license to Papillon. As a result, the U.S. government may have certain rights to intellectual property embodied in our AVR-RD-04 program, or in other product candidates to the extent funded by the U.S. government pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show

that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply. Any exercise by the government of certain of its rights could harm our competitive position, business, financial condition, results of operations and prospects. With respect to state funding, specifically funding via the California Institute of Regenerative Medicine, or CIRM, which has granted funds to UCSD for the study of AVR-RD-04 for cystinosis, the grantee has certain obligations and the state or CIRM has certain rights. For example, the grantee has an obligation to share intellectual property, including research results, generated by CIRM-funded research, for research use in California.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

Changes in either the patent laws or the interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes several significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

The patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Two cases involving diagnostic method claims and "gene patents" were decided this year by the Supreme Court of the United States, or Supreme Court. On March 20, 2012, the Supreme Court issued a decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., or Prometheus, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as "administering" or "determining" steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. On July 3, 2012, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. On June 13, 2013, the Supreme Court issued its decision in Association for Molecular Pathology v. Myriad Genetics, Inc., or Myriad, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. Myriad held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent-eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible. On March 4, 2014, the USPTO issued a guidance memorandum to patent examiners entitled 2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products. These guidelines instruct USPTO examiners on the ramifications of the Prometheus and Myriad rulings and apply the Myriad ruling to natural products and principles including all naturally occurring nucleic acids.

Certain claims of our licensed patents and patent applications contain, and any future patents we may obtain may contain, claims that relate to specific recombinant DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties. In addition, the 2014 USPTO guidance could impact our ability to pursue similar patent claims in patent applications we may prosecute in the future.

We cannot assure you that our efforts to seek patent protection for our product candidates will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court's decisions in Prometheus and Myriad may have on the ability of life science companies to obtain or enforce patents relating to their products in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent rights and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court has held in Myriad that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter. Such outcomes could harm our business, financial condition, results of operations or prospects.

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

Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, one or more U.S. patents that we license or may own or license in the future, if any, 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. 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. A patent may only be extended once and only based on a single approved product. However, we may not be granted an extension because of, 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 revenue could be reduced, possibly materially. In addition, we do not control the efforts of our licensors to obtain a patent term extension, and there can be no assurance that they will pursue or obtain such extensions to the patents that we license from them.

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.

We have registered the marks "AVROBIO" and "plato" with the USPTO and in certain other countries, but we do not have trademarks or trademark applications with the USPTO for the marks "AVRO" or the AVROBIO logo. In the future, even if we apply for registration of these marks, there can be no assurance that such registration will be approved. Once registered, our 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 financial condition or results of operations.

Intellectual property rights and regulatory exclusivity 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 gene therapy products that are similar to our product candidates but that are not covered by the claims of the patents that we license or may own or license in the future;
- we, our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patents or pending patent applications that we license or may own or license in the future;
- we, 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 our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own or license in the future will not lead to issued patents;
- issued patents that we hold rights to or may hold rights to in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- one or more of our product candidates may never be protected by patents;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may have an adverse effect on our business; and
- we may choose not to file a patent application for certain trade secrets or know-how, and a third party may subsequently file a patent application or obtain a patent covering such intellectual property.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

Risks related to ownership of our common stock

The market price of our common stock may be highly volatile, and you may not be able to resell your shares at or above the price at which you purchased our shares.

Our stock price is likely to be volatile. Since our initial public offering, or IPO, in June 2018, through March 1, 2023, the trading price of our common stock has ranged from $53.70 to $0.56. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the price at which you purchased shares. The market price for our common stock may be influenced by many factors, including:

- the ongoing COVID-19 pandemic;
- adverse results or delays in ongoing or planned preclinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical studies of such products;
- an inability to obtain additional funding;
- failure by us to comply with the terms of our Term Loan Agreement;
- failure by us to successfully develop and commercialize our product candidates;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;

- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial projections we may provide to the public;
- failure by us to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partners or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel, or other skilled personnel;
- significant lawsuits, including patent or stockholder litigation;
- changes in the market valuations of similar companies;
- sales of our common stock by us or our stockholders in the future; and
- the trading volume of our common stock.

In addition, companies trading in the stock market in general, and Nasdaq in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

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

Prior to our IPO in June 2018, there had been no public market for our common stock. Although our common stock is listed on Nasdaq , an active trading market for our shares may never be sustained. If an active market for our common stock is not sustained, it may be difficult for you to sell shares you purchased without depressing the market price for the shares, or at all.

An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling additional shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. Although we have obtained research coverage from certain analysts, there can be no assurance that analysts will continue to cover us or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price would

likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Based on shares outstanding as of March 16, 2023, our executive officers, directors, five percent stockholders and their affiliates beneficially owned approximately 32% of our voting stock. As a result, if these stockholders were 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, acting together, may be able to influence elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders. Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below the current trading price of our stock and have held their shares for a longer period, they may be more interested in selling our Company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other stockholders. Additionally, from time to time, any of our non-affiliated shareholders may accumulate or acquire significant positions in our common stock and may similarly be able to influence our business or matters submitted to our stockholders for approval.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the JOBS Act. We will remain an EGC until the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1.235 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the completion of our IPO; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the first day of the year following the first year in which the market value of our common stock that is held by non-affiliates exceeds $700 million as of June 30 in any given year. 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 emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's discussion and analysis of financial condition and results of operations" disclosure;
- reduced disclosure obligations regarding executive compensation; and
- an exemption from the requirement to seek nonbinding advisory votes on executive compensation or golden parachute arrangements.

We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this Annual Report on Form 10-K. In particular, we have not included in this Annual Report, and do not intend to include in our 2023 Proxy Statement, all of the executive compensation information that would be required if we were not an EGC. 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.

In addition, the JOBS Act provides that an EGC may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" if the market value of our common stock held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of June 30 in any given year, which would allow us to take advantage of many of the same exemptions from disclosure requirements.

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

As a public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and will continue to make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and increasingly more expensive for us to obtain and maintain director and officer liability insurance.

Pursuant to Section 404, we are required to furnish a report by our management on our internal control over financial reporting, and, once we are no longer an EGC or a "smaller reporting company," we will be required to furnish an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404, we continue to be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially continue to engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude that our internal control over financial reporting is effective as required by Section 404. This 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, are 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 may 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 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 or a "smaller reporting company," 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 could be an EGC for up to five years following the completion of our IPO and will qualify as a "smaller reporting company" if the market value of our common stock held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of June 30 in any given year. An independent assessment of the effectiveness of our internal control over financial reporting could detect problems that our management's assessment might not. 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.

If we experience material weaknesses or deficiencies in the future, or otherwise fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our stock price.

We expect to continue our efforts to improve our control processes, though there can be no assurance that our efforts will ultimately be successful or avoid potential material weaknesses, and we expect to continue incurring additional costs as a result of these efforts. If we are unable to successfully remediate any material weaknesses in our internal control over financial reporting, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our stock price may decline as a result. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

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

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.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to drop significantly.

Sales of a substantial number of shares of our common stock in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that 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, holders of an aggregate of approximately 4.5 million shares of our common stock will have rights, subject to certain 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. In addition, shares reserved for issuance upon the exercise of stock options outstanding under our equity incentive plans will become eligible for sale in the public market in the future. We have registered all shares of common stock that we may issue under our equity compensation plans, which can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

We do not intend to pay dividends on our common stock, so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock. For example, our Term Loan Agreement restricts our ability to pay certain kinds of dividends or to make certain kinds of distributions on account of our capital stock, and we may enter into agreements in the future with similar restrictions. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Provisions in our amended and restated certificate of incorporation and by-laws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize “blank check” preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;

- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated by-laws; and require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated by-laws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Our bylaws contain exclusive forum provisions, which may limit a stockholder's ability to bring a claim in a judicial forum it finds favorable and may discourage lawsuits with respect to such claims.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any state law claim for (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of or based on a fiduciary duty owed by any of our current or former directors, officers or other employees to us or our stockholders; (3) any action asserting a claim against us or any of our current or former directors, officers, employees or stockholders arising pursuant to any provision of the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws; or (4) any action asserting a claim governed by the internal affairs doctrine, or the Delaware Forum Provision. The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act or the Exchange Act. Our amended and restated bylaws further provide that, unless we consent in writing to an alternative forum, the United States District Court for the District of Massachusetts will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or the Federal Forum Provision, as our principal executive offices are located in Cambridge, Massachusetts. In addition, our amended and restated bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock is deemed to have notice of and consented to the foregoing Delaware Forum Provision and the Federal Forum Provision; provided, however, that stockholders cannot and will not be deemed to have waived our compliance with the U.S. federal securities laws and the rules and regulations thereunder.

We recognize that the Delaware Forum Provision and the Federal Forum Provision may impose additional litigation costs on stockholders in pursuing any such claims, particularly if the stockholders do not reside in or near the State of Delaware or the Commonwealth of Massachusetts. Additionally, these forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to bring a claim in a judicial forum that they 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 even though an action, if successful, might benefit our stockholders. Section 22 of the Securities Act creates a concurrent jurisdiction for state and federal courts over all suits brought concerning a duty or liability created by the securities laws, rules and regulations thereunder. While the Delaware Supreme Court and other state courts have upheld the validity of federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert the provision is unenforceable, and if the Federal Forum Provision is found to be unenforceable, we may incur additional costs with resolving such matters. The Court of Chancery of the State of Delaware and the United States District Court for the District of Massachusetts may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

Our failure to meet Nasdaq's continued listing requirements could result in a delisting of our common stock.

If we fail to satisfy the continued listing requirements of Nasdaq, such as the corporate governance requirements or the requirement to maintain a minimum bid price of $1.00 per share pursuant to Nasdaq Listing Rule 5450(a)(1), or the Minimum Bid Price Requirement, Nasdaq may take steps to delist our common stock.

On October 4, 2022, we received a written notice from the staff, or the Staff, of Nasdaq's Listing Qualifications Department, notifying us that, for the 30 consecutive business day period between August 22, 2022 through October 3, 2022, our common stock had not complied with the Minimum Bid Price Requirement. Nasdaq's written notice did not result in the immediate delisting of our common stock from Nasdaq. In accordance with Nasdaq Listing Rule 5810(c)(3)(A), the Company had 180 calendar days, or until April 3, 2023, or the Compliance Date, to regain compliance with the Minimum Bid Price Requirement.

On February 23, 2023, we received a written notice from the Staff notifying us that for 10 consecutive business days, from February 8, 2023 to February 22, 2023, the closing bid price of our common stock was at $1.00 per share or greater. Accordingly, the Staff advised us that we had regained compliance with the Minimum Bid Price Requirement and indicated that the matter was now closed.

While we have regained compliance with the Minimum Bid Price Requirement as of the date of this Annual Report, we can provide no assurance that we will continue to remain in compliance with the Minimum Bid Price Requirement. If we are unable to maintain compliance with any of Nasdaq's continued listing requirements in the future, we may be subject to delisting. At that time, we may appeal the Staff's delisting determination to a Nasdaq Hearing Panel. There can no assurance that, if we receive a delisting notice and appeal the delisting determination by the Staff to the Nasdaq Hearing Panel, such appeal would be successful.

Such a delisting would likely have a negative effect on the price of our common stock and would impair your ability to sell or purchase our common stock when you wish to do so. Any such delisting could also adversely impact our ability to raise additional capital or enter into strategic transactions. Additionally, if our common stock is not listed on, or becomes delisted from, Nasdaq for any reason, trading our common stock could be conducted only in the over-the-counter, or OTC, market or on an electronic bulletin board established for unlisted securities such as the OTC Bulletin Board, an inter-dealer automated quotation system for equity securities that is not a national securities exchange, and the liquidity and price of our common stock may be more limited than if we were quoted or listed on Nasdaq or another national securities exchange. In such circumstances, you may be unable to sell your common stock unless a market can be established or sustained.

General Risk Factors

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. For example, the COVID-19 pandemic has caused extreme volatility and disruptions in the capital and credit markets. In addition, Russia's invasion of Ukraine may lead to a prolonged, adverse impact on global economic, social and market conditions. A severe or prolonged economic downturn could result in a variety of risks to our business, including weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. For example, while we do not have any current operations in Ukraine or Russia, we do not know the extent to which Russia's invasion of Ukraine could impact any of our current suppliers and their ability to provide us with supplies and services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business, financial condition, results of operations and prospects.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and

business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite our security measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. For example, in 2017 we were subjected to a cyberattack by a third party, which led to the theft of a portion of our funds. We implemented remedial measures promptly following this breach and do not believe that this breach had a material adverse effect on our business. In addition, in February 2019, one of our vendors was subject to a cyberattack by a third party, which resulted in the payment by us of a fraudulent invoice. We have implemented remedial measures following this breach and do not believe that this breach had a material effect on our business. However, if any cyberattack or data breach were to occur in the future and cause interruptions in our or our collaborators', contractors' or consultants' operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our business data, trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. 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 or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Changes in tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our corporate headquarters are located in Cambridge, Massachusetts, and encompasses a total of approximately 26,114 square feet of leased office space and laboratory facilities, pursuant to a sub-sublease. We initially entered into the sub-sublease for 13,643 square feet of laboratory space, or the Lab Sublease, in August 2018. The Lab Sublease was set to expire in April 2022. In January 2022, we amended the Lab Sublease to increase the premises to a total of 26,114 square feet and extend the term through April 30, 2023, and we have thereafter agreed to extend the Lab Sublease through April 30, 2024. In June 2020, we entered into a lease agreement for 3,885 square feet of office space located in Toronto, Ontario, Canada, which expires in June 2025. In October 2022, we subleased the entirety of the Toronto leased office space to a third party for a term extending through June 2025. We believe that our office and laboratory space is sufficient to meet our current needs and that suitable additional space or alternative space will be available as needed on commercially reasonable terms.

Item 3. Legal Proceedings.

From time to time, we are subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, as of the date of this Annual Report on Form 10-K, we are not presently subject to any pending or threatened litigation that we believe, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us 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 the Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information

Our common stock is traded on the Nasdaq Global Select Market under the symbol "AVRO". Trading of our common stock commenced on June 21, 2018, following the completion of our initial public offering. Prior to that time, there was no established public trading market for our common stock.

Holders of Common Stock

As of March 10, 2023, the number of holders of record of our common stock was eight. The number of holders is based upon the actual number of holders registered in our records at such date and excludes holders in "street name" or persons, partnerships, associations, corporations, or other entities identified in security positions listings maintained by depository trust companies.

Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors and will depend on, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors may deem relevant. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Securities Authorized for Issuance under Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities; Use of Proceeds from Registered Offerings

We did not sell any unregistered equity securities during the period covered by this Annual Report on Form 10-K.

Item 6. [Reserved]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

Our management's discussion and analysis of our financial condition and results of operations are based upon our consolidated financial statements included in this Annual Report on Form 10-K, which have been prepared by us in accordance with United States generally accepted accounting principles, or GAAP, and with Regulation S-X promulgated under the Securities Exchange Act of 1934, as amended. This discussion and analysis should be read in conjunction with the consolidated financial statements and the notes thereto included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in Part I, Item 1A. Risk Factors of this Annual Report on Form 10-K, 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.

Overview

We are a clinical-stage gene therapy company with a purpose to free people from a lifetime of genetic disease. Our company is focused on developing potentially curative HSC gene therapies to treat patients with rare diseases following a single dose treatment regimen. Our gene therapies employ HSCs that are harvested from the patient and then modified with a lentiviral vector to insert the equivalent of a functional copy of the gene that is mutated in the target disease. We believe that our approach, which is designed to transform stem cells from patients into therapeutic products, has the potential to provide curative benefit for a range of diseases. Our initial focus is on a group of rare genetic diseases referred to as lysosomal disorders, some of which today are primarily managed with enzyme replacement therapies, or ERTs. These lysosomal disorders have well-understood biologies, identified patient populations, established standards of care yet with significant unmet needs, and represent large market opportunities with approximately $3.5 billion in worldwide net sales in 2022.

Our pipeline is comprised of four HSC gene therapy programs: AVR-RD-02 for the treatment of Gaucher disease type 1 and type 3; AVR-RD-04 for the treatment of cystinosis; AVR-RD-05 for the treatment of neuronopathic mucopolysaccharidosis type II, or MPS-II or Hunter syndrome; and AVR-RD-03 for the treatment of Pompe disease.

AVR-RD-02 is currently being studied for the treatment of Gaucher disease type 1 in a Company-sponsored Phase 1/2 clinical trial, which we refer to as the Guard1 clinical trial. As of March 20, 2023, four patients have been dosed in the Guard1 clinical trial, and six patients have been enrolled. We are actively recruiting additional potential patients for our currently active Guard1 trial sites. We are also planning for a registrational global Phase 2/3 clinical trial of AVR-RD-02 for the treatment of Gaucher disease type 3, which we refer to as the Guard3 clinical trial. We currently are planning for the Guard3 clinical trial to be initiated in the second half of 2023, subject to regulatory alignment.

AVR-RD-04 is currently being studied for the treatment of cystinosis by our collaborators at UCSD in a Phase 1/2 collaborator-sponsored clinical trial. Enrollment of this clinical trial is complete with a total of six patients dosed. In addition, based on recent regulatory interactions and feedback and subject to regulatory clearance, we are planning to initiate activities for a Company-sponsored Phase 1/2 clinical trial of AVR-RD-04 for the treatment of cystinosis in the second half of 2023, which is designed to be registration-enabling.

AVR-RD-05 is being studied for the treatment of Hunter syndrome by our collaborators at The University of Manchester, and we currently expect the Phase 1/2 collaborator-sponsored clinical trial will be initiated in 2023.

AVR-RD-03 is our preclinical program for Pompe disease. While we continue to advance AVR-RD-03, we are prioritizing our Gaucher disease and cystinosis clinical programs. As a result, we no longer expect to initiate a clinical trial for AVR-RD-03 in 2023.

In January 2022, we announced the deprioritization of AVR-RD-01, our investigational gene therapy program for Fabry disease. This decision was made due to several factors, including new clinical data showing variable engraftment patterns from the five most recently dosed patients in the Company's Phase 2 clinical trial of AVR-RD-01 for the treatment of Fabry disease, which we refer to as the FAB-GT clinical trial. As a result of the deprioritization, the Company stopped enrollment of its Phase 2 FAB-GT clinical trial and continues to focus on its other pipeline programs.

Since our inception in 2015, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, acquiring or discovering product candidates and securing related intellectual property rights, conducting discovery, research and development activities for our programs and planning for potential commercialization. To date, we have not generated any product revenue and have financed our operations primarily through

the private placement of our securities and through public offerings of our common stock. Through December 31, 2022, we had received gross cash proceeds of $87.5 million from sales of our preferred stock; gross cash proceeds, before deducting underwriting discounts and commissions and expenses, of $428.1 million from sales of our common stock through our initial public offering and follow-on offerings; and gross cash proceeds, before deducting commissions and expenses, of $23.5 million from sales of our common stock through our 2019 "at-the-market" facility, or 2019 ATM Facility.

Additionally, we have incurred significant operating losses. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of one or more of our current or future product candidates and programs. Our net losses were $105.9 million and $119.1 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $489.4 million. We expect to continue to incur significant expenses for at least the next several years as we advance our current and future product candidates from discovery through preclinical development and clinical trials and seek regulatory approval of our product candidates. Our pipeline consists of four investigational gene therapies, two of which are currently in clinical development. As a result, further development of these programs will require us to expend significant resources to advance these candidates. 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. We may also incur expenses in connection with the in-licensing or acquisition of additional product candidates.

We will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations with proceeds from outside sources, with a majority of such proceeds to be derived from sales of equity, including the net proceeds from our follow-on offerings and sales of common stock under our 2019 ATM Facility as well as proceeds under our Term Loan Agreement. We may also pursue additional funding from outside sources, including our expansion of, or our entry into, new borrowing arrangements; research and development incentive payments from the Australian government; and our entry into potential future collaboration agreements for one or more of our programs. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of one or more of our product candidates or delay our pursuit of potential in-licenses or acquisitions.

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 or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, 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 and cash equivalents of $92.6 million. We believe that our existing cash and cash equivalents as of December 31, 2022 will enable us to fund our operating expenses and capital expenditure requirements into the first quarter of 2024. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See "*Liquidity and Capital Resources.*" To finance our operations beyond that point, we will need to raise additional capital, which cannot be assured.

Components of Our Consolidated Results of Operations

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred in connection with the discovery and development of our product candidates. We expense research and development costs as incurred. These expenses consist of costs incurred in connection with the development of our product candidates, including:

- license maintenance fees and milestone fees incurred in connection with various license agreements;
- expenses incurred under agreements with contract research organizations, or CROs, contract manufacturing organizations, or CMOs, as well as investigative sites and consultants that conduct our clinical trials, preclinical studies and other scientific development services;
- manufacturing scale-up expenses and the cost of acquiring and manufacturing preclinical and clinical trial materials and commercial materials, including manufacturing validation batches;

- costs of purchasing lab supplies and non-capital equipment used in our preclinical activities;
- employee-related expenses, including salaries, related benefits, travel and stock-based compensation expense for employees engaged in research and development functions;
- costs related to compliance with regulatory requirements; and
- allocated facilities costs, depreciation and other expenses, which include rent and utilities.

We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers.

Our direct research and development expenses are tracked on a program-by-program basis for our product candidates and consist primarily of external costs, such as fees paid to outside consultants, CROs, CMOs, and central laboratories in connection with our preclinical development, process development, manufacturing and clinical development activities. Our direct research and development expenses by program also include fees incurred under license agreements. We do not allocate employee costs or facility expenses, including depreciation or other indirect costs, to specific programs because these costs are deployed across multiple programs and, as such, are not separately classified. We use internal resources primarily to oversee the research and discovery as well as for managing our preclinical development, process development, manufacturing and clinical development activities. These employees work across multiple programs and, therefore, we do not track their costs by program.

The table below summarizes our research and development expenses related to our product candidates (in thousands):

	Year Ended December 31,	
	2022	2021
Fabry	$ 9,644	$ 12,402
Gaucher	8,662	6,748
Pompe	830	3,073
Cystinosis	4,615	5,104
Hunter	4,968	2,294
Other research activities	105	199
Unallocated research and development expenses	43,362	53,294
Total research and development expenses	$ 72,186	$ 83,114

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. As a result, we expect that our research and development expenses will increase substantially over the next several years, particularly as we increase personnel costs, including stock-based compensation, contractor costs and facilities costs, as we continue to advance the development of our product candidates. We also expect to incur additional expenses related to milestone and royalty payments payable to third parties with whom we have entered into license agreements to acquire the rights to our product candidates.

The successful development and commercialization of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any of our product candidates or when, if ever, material net cash inflows may commence from any of our product candidates. This uncertainty is due to the numerous risks and uncertainties associated with product development and commercialization, including the uncertainty of:

- the scope, progress, outcome and costs of our preclinical development activities, clinical trials and other research and development activities;
- establishing an appropriate safety profile with IND-enabling studies;
- successful patient enrollment in, and the design, initiation and completion of, clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;

- development and timely delivery of commercial-grade drug formulations that can be used in our clinical trials and for commercial launch;
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- significant and changing government regulation;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others;
- maintaining a continued acceptable safety profile of the product candidates following approval; and
- the risks disclosed in the section entitled "Risk Factors" of this Annual Report on Form 10-K.

We may never succeed in achieving regulatory approval for any of our product candidates. We may obtain unexpected results from our clinical trials. We may elect to discontinue, delay or modify clinical trials of some product candidates or focus on others. Any changes in the outcome of any of these variables with respect to the development of our product candidates in preclinical and clinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if the FDA, or another regulatory authority were to delay our planned start of clinical trials or require us to conduct clinical trials or other testing beyond those that we currently expect, or if we experience significant delays in enrollment in any of our planned clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of that product candidate. 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.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, related benefits, travel and stock-based compensation expense for personnel in executive, finance and administrative functions. General and administrative expenses also include professional fees for legal, consulting, accounting and audit services.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates. We also anticipate that we will continue to incur increased accounting, audit, legal, compliance, director and officer insurance costs as well as investor and public relations expenses associated with being a public company. We anticipate the additional costs for these services will substantially increase our general and administrative expenses. Additionally, if and when we believe a regulatory approval of a product candidate appears likely, we anticipate an increase in payroll and other commercialization-related expenses as a result of our preparation for commercial operations, especially as it relates to the sales and marketing of our product candidate.

Other (Expense) Income, net

Other (expense) income, net primarily consists of interest income earned on our cash and cash equivalents, changes in foreign currency, and interest expense related to our Term Loan Agreement.

Consolidated Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

The following table summarizes our consolidated results of operations (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Operating expenses:			
Research and development	$ 72,186	$ 83,114	$ (10,928)
General and administrative	33,248	35,727	(2,479)
Total operating expenses	105,434	118,841	(13,407)
Loss from operations	(105,434)	(118,841)	13,407
Other (expense) income:			
Interest (expense) income, net	(299)	(224)	(75)
Other expense	(157)	(61)	(96)
Total other (expense) income, net	(456)	(285)	(171)
Net loss	$ (105,890)	$ (119,126)	$ 13,236

Research and Development Expenses

Research and development expenses decreased by $10.9 million to $72.2 million for the year ended December 31, 2022, from approximately $83.1 million for the year ended December 31, 2021. This decrease was driven by a $9.7 million decrease in personnel-related costs which was impacted by our reduction in workforce implemented in January 2022, a $2.6 million decrease in our preclinical costs, and a $1.6 million decrease in manufacturing costs. These decreases were partially offset by a $2.1 million increase in development costs and a $0.8 million increase in consulting costs.

General and Administrative Expenses

General and administrative expenses decreased by $2.5 million to $33.2 million for the year ended December 31, 2022, from $35.7 million for the year ended December 31, 2021. This decrease was attributable to $1.8 million decrease in personnel-related costs which was impacted by our reduction in workforce implemented in January 2022 and a $0.7 million decrease in professional fees.

Other (Expense) Income, net

Other (expense) income, net was $(0.5) million for the year ended December 31, 2022, compared to $(0.3) million of other income, net for the year ended December 31, 2021. The increase in expense was driven by a $1.6 million increase in interest expense related to our Term Loan Agreement, which we entered into in the fourth quarter of 2021 and partially offset by a $1.5 million increase in interest income earned on short-term money market funds.

Liquidity and Capital Resources

Since our inception, we have not generated any revenue and have incurred significant operating losses and negative cash flows from our operations. We have funded our operations to date primarily with proceeds from the sale of preferred stock and our common stock through our initial public offering, or IPO, and we have raised additional capital through subsequent follow-on offerings and our 2019 ATM Facility, as well as through our Term Loan Agreement. Through December 31, 2022, we had received gross cash proceeds of $87.5 million from sales of our preferred stock; gross cash proceeds, before deducting underwriting discounts and commissions and expenses, of $428.1 million from sales of our common stock through our IPO and follow-on public offerings; $23.5 million in gross proceeds from the sale of our common stock under our 2019 ATM Facility; and we had drawn $15.0 million in term loans under our Term Loan Agreement.

On July 1, 2019, we filed a shelf registration statement on Form S-3 with the SEC, or the July 2019 Shelf, which covers the offering, issuance and sale by us of up to an aggregate of $200.0 million of our common stock, preferred stock, debt securities, warrants and/or units. We simultaneously entered into a Sales Agreement with Cowen and Company, LLC, as sales agent, to provide for the offering, issuance and sale by us of up to $50.0 million of our common stock from time to time in “at-the-market” offerings under the July 2019 Shelf. The July 2019 Shelf was declared effective by the SEC on July 10, 2019.

On December 20, 2019, we filed a shelf registration statement on Form S-3 with the SEC, or the December 2019 Shelf, which covers the offering, issuance and sale by us of up to an aggregate of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units. The December 2019 Shelf was declared effective by the SEC on January 14, 2020.

In July 2019, we closed an underwritten public offering, or the July 2019 Follow-On Offering, under the July 2019 Shelf of 7,475,000 shares of our common stock at a public offering price of $18.50 per share, which included 975,000 shares of our common stock resulting from the full exercise of the underwriters' option to purchase additional shares at the public offering price, less underwriting discounts and commissions. The net proceeds to us from this offering, after deducting underwriting discounts and commissions and other offering expenses payable by us, were $129.5 million.

In February 2020, we closed an underwritten public offering, or the February 2020 Follow-On Offering, under the December 2019 Shelf of 4,350,000 shares of our common stock at a public offering price of $23.00 per share, less underwriting discounts and commissions. The net proceeds to us from this offering, after deducting underwriting discounts and commissions and other offering expenses payable by us, were $93.6 million.

In June 2020, we sold an aggregate of 384,140 shares of common stock under the 2019 ATM Facility for net proceeds, after deducting commissions and other offering expenses payable by us, of $8.1 million.

In November 2020, we closed an underwritten public offering, or the November 2020 Follow-On Offering, of 5,000,000 shares of our common stock at a public offering price of $15.00 per share, less underwriting discounts and commissions. The net proceeds to us from the November 2020 Follow-On Offering, after deducting underwriting discounts and commissions and other offering expenses payable by us, were $70.2 million.

In May 2021, we sold an aggregate of 1,829,268 shares of common stock under the 2019 ATM Facility for net proceeds, after deducting commissions and other offering expenses payable by us, of $14.5 million. As of December 31, 2022, approximately $26.5 million of common stock remained available for future issuance under the 2019 ATM Facility.

On November 2, 2021, or the Closing Date, we entered into the Term Loan Agreement. The Term Loan Agreement provided for (i) on the Closing Date, $30.0 million aggregate principal amount of term loans available through October 31, 2023; (ii) an additional $20.0 million in term loan facilities available through October 31, 2023 upon the achievement of certain regulatory or clinical milestones prior to the time of draw, or the Milestone Funding; and (iii) an additional discretionary $15.0 million term loan facility available upon our request and approval by the Agent and the Lenders, or, collectively, the Term Loans. We drew $15.0 million in term loans on the Closing Date. As a result of the deprioritization of our Fabry disease program, we are no longer able to draw the $20.0 million of Milestone Funding per the terms of the Term Loan Agreement. The loan repayment schedule provides for interest only payments until November 1, 2024, followed by consecutive monthly payments of principal and interest. All unpaid principal and accrued and unpaid interest with respect to each term loan is due and payable in full on October 1, 2026.

In July 2022, the July 2019 Shelf expired, and on November 8, 2022, we filed a shelf registration statement on Form S-3 with the SEC, or the November 2022 Shelf, which covers the offering, issuance and sale by us of up to an aggregate of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units. The December 2019 Shelf expired in December 2022, and the November 2022 Shelf carried forward unsold securities previously covered by the December 2019 Shelf, thus registering an aggregate total of $250.0 million of our common stock, preferred stock, debt securities, warrants and/or units. Because the 2019 ATM Facility was established under the July 2019 Shelf that has expired, in connection with the November 2022 Shelf, we simultaneously entered into a new Sales Agreement with Cowen and Company, LLC, as sales agent, to provide for the offering, issuance and sale by us of up to $50.0 million of our common stock from time to time in "at-the-market" offerings under the November 2022 Shelf (the "2022 ATM Facility"). As of the date of this report, we have not made any sales under the 2022 ATM Facility, and intend to file one or more prospectuses or prospectus supplements related to this new facility before making any such sales.

As of December 31, 2022, we had cash and cash equivalents of $92.6 million. Cash in excess of immediate requirements is invested primarily with a view to liquidity and capital preservation. We believe that our existing cash and cash equivalents as of December 31, 2022 will enable us to fund our operating expenses and capital expenditure requirements into the first quarter of 2024. See "Risk Factors" for risks related to our business, financial position and need for additional capital.

Cash Flows

The following table summarizes our cash flows for each of the periods presented (in thousands):

	Year Ended December 31,	
	2022	2021
Net cash used in operating activities	$ (97,208)	$ (98,025)
Net cash used in investing activities	(267)	(2,461)
Net cash provided by financing activities	262	30,371
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (97,213)	$ (70,115)

Operating Activities

During the year ended December 31, 2022, operating activities used $97.2 million of cash and cash equivalents, resulting from our net loss of $105.9 million and cash used by changes in our operating assets and liabilities of $7.4 million which was offset by non-cash charges of $16.1 million. Net cash used by changes in our operating assets and liabilities for the year ended December 31, 2022 consists primarily of a $2.5 million decrease in prepaid expenses and other current assets, a $3.9 million decrease in accrued expenses and other current liabilities, a $3.1 million decrease in accounts payable, and a $2.9 million decrease in current and non-current operating lease liabilities. The increase in accrued expenses and other current liabilities was primarily due to an increase in accrued compensation and benefit costs.

During the year ended December 31, 2021, operating activities used $98.0 million of cash and cash equivalents, resulting from our net loss of $119.1 million, partially off-set by net cash provided by changes in our operating assets and liabilities of $1.3 million and non-cash charges of $19.8 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2021 consists primarily of a $2.1 million increase in accrued expenses and other current liabilities, a $0.4 million decrease in other assets, and a $0.8 million increase in accounts payable, partially offset by a $2.0 million increase in prepaid expenses and other current assets. The increase in accrued expenses and other current liabilities was primarily due to an increase in accrued compensation and benefit costs.

Investing Activities

Net cash used in investing activities was $0.3 million for the year ended December 31, 2022 compared to $2.5 million for the year ended December 31, 2021. The decrease in cash used in investing activities was primarily due to a decrease in purchases of property and equipment.

Financing Activities

Net cash provided by financing activities was $0.3 million for the year ended December 31, 2022 compared to $30.4 million for the year ended December 31, 2021. The decrease in cash provided by financing activities was primarily due to the proceeds of $15.0 million from long-term debt, proceeds of $14.6 million from issuance of common shares under our 2019 ATM facility, net of offering costs paid, and $0.9 million from proceeds from the exercise of stock options during the year ended December 31, 2021 which was partially offset by $0.2 million in proceeds from the issuance of shares under our 2018 Employee Stock Purchase Plan and $0.1 million in proceeds from the exercise of stock options during the year ended December 31, 2022.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates. Our expenses will also increase as we:

- continue our development of our product candidates, including enrollment and dosing of patients in our ongoing clinical trials;
- initiate additional clinical trials and preclinical studies for our other current and future product candidates;
- seek to identify and develop or in-license or acquire additional product candidates and technologies;
- seek to industrialize our HSC gene therapy approach into a robust, scalable and, if approved, commercially viable process;
- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we may obtain marketing approval;
- hire and retain additional personnel, such as clinical, quality control, and scientific personnel;
- expand our infrastructure, office space and facilities to accommodate our employee base, including adding equipment and physical infrastructure to support our research and development; and
- continue to incur additional public company-related costs.

We believe that our $92.6 million of existing cash and cash equivalents as of December 31, 2022, will enable us to fund our operating expenses and capital expenditure requirements into the first quarter of 2024. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. If we receive regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution, depending on where we choose to commercialize.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaboration agreements, government and other third-party funding, strategic alliances, licensing arrangements or marketing and distribution arrangements. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through government and other third-party funding, collaboration agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2022 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods (in thousands):

	Payments Due by Period				
	Total	Less than 1 Year	1 to 3 Years	4 to 5 Years	More than 5 Years
Operating lease commitments (1)	$ 1,214	$ 1,007	$ 207	$ —	$ —
Total	$ 1,214	$ 1,007	$ 207	$ —	$ —

(1) Represents future minimum lease payments under our non-cancelable operating leases for office and laboratory space, which are located in Cambridge, Massachusetts and Toronto, Canada. Those leases will expire from April 2024 to June 2025. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the preceding table as the amount and timing of such payments are not known.

In addition, pursuant to our license agreements with UHN, BioMarin, The University of Manchester, Papillon and the Lund University rights holders, we are required to make certain milestone and royalty payments to our licensors. See "Business—License Agreements" for additional details regarding our payment obligations to these licensors.

Critical Accounting Policies and Significant Judgments and Estimates

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

While our significant accounting policies are described in more detail in Note 2 *"Summary of Significant Accounting Policies"* to our consolidated financial statements appearing elsewhere in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Accrued Research and Development Expenses

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 cost incurred for the service when we have not yet been invoiced or otherwise notified of 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 the consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of these estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- vendors, including central laboratories, in connection with preclinical development activities;
- CROs and investigative sites in connection with preclinical and clinical studies; and
- CMOs in connection with drug substance and drug product formulation of preclinical and clinical trial materials.

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple research institutions and CROs that conduct and manage preclinical studies and clinical trials on our behalf. 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. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. 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 the amount of prepaid expenses 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. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Stock-Based Compensation

We measure stock options and other stock-based awards granted to employees and members of our board of directors for their services as directors based on the fair value on the date of the grant and recognize the corresponding compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. We have issued stock options, restricted stock and restricted stock units with service-based vesting conditions.

Modifications to stock-based awards are treated as an exchange of the original award for a new award with total compensation equal to the grant-date fair value of the original award plus any incremental value of the modification. The incremental value is based on the excess of the fair value of the modified award over the fair value of the original award immediately before the modification.

Prior to the adoption of Accounting Standards Update (ASU) No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting (ASU 2018-07)*, as discussed in Note 2 *"Summary of Significant Accounting Policies"* to our consolidated financial statements appearing elsewhere in this Annual Report, the measurement date for non-employee awards was generally the date the services were completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After the adoption of ASU 2018-07, the measurement date for non-employee awards is the later of the adoption date of ASU 2018-07, or the date of grant, without change in the fair value of the award.

We estimate the fair value of each stock option grant using the Black-Scholes option-pricing model, which uses as inputs the estimated fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield.

We determined the assumptions for the Black-Scholes option-pricing model as discussed below. Each of these inputs is subjective and generally requires significant judgment to determine.

- *Determination of the Fair Value of Common Stock.* The fair value of our common stock is determined based on the quoted market price of our common stock. Prior to our IPO, there was no public market for our common stock, and consequently, the estimated fair value of our common stock was determined by our board of directors as of the date of each option grant, with input from management, considering third-party valuations of our common stock as well as our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation. Following the closing of our IPO, it was no longer necessary for our board of directors to estimate the fair market value of our common stock in connection with our accounting for granted equity awards.
- *Expected Term.* The expected term represents the period that the stock-based awards are expected to be outstanding. The expected term of stock options granted has been determined using the simplified method, which uses the midpoint between the vesting date and the contractual term.
- *Risk-Free Interest Rate.* The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the date of grant for zero-coupon U.S. Treasury constant maturity notes with terms approximately equal to the stock-based award's expected term.
- *Expected Volatility.* Because we do not have long-term trading history of our common stock, the expected volatility was derived from the average historical stock volatilities of several public companies within our industry that we consider to be comparable to our business over a period equivalent to the expected term of the stock-based awards.
- *Dividend Rate.* The expected dividend is zero as we have not paid and do not anticipate paying any dividends in the foreseeable future.

If any of the assumptions used in the Black-Scholes model change significantly, stock-based compensation for future awards may differ materially compared with the awards granted previously.

Emerging Growth Company Status

We are an "emerging growth company," as defined in the JOBS Act, and we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. We may take advantage of these exemptions until we are no longer an emerging growth company. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. We have elected to use the extended transition period for complying with new or revised accounting standards and, as a result of this election, our financial statements may not be comparable to companies that comply with public company effective dates. We may take advantage of these exemptions up until the last day of the fiscal year following the fifth anniversary of our IPO or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1.235 billion in annual revenue, we have more than $700.0 million in market value of our stock held by non-affiliates or we issue more than $1.0 billion of non-convertible debt securities over a three-year period.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the Securities and Exchange Commission.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 *"Summary of Significant Accounting Policies"* to our audited financial statements appearing elsewhere in this Annual Report.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Interest Rate Risk

As of December 31, 2022, we had cash and cash equivalents of $92.6 million, which consisted of cash and money market funds. Interest income is sensitive to changes in the general level of interest rates; however, due to the nature of these investments, an immediate 10% change in interest rates would not have a material impact on our cash and cash equivalents, debt-related obligations, financial position or results of operations.

Foreign Currency Exchange Risk

We are exposed to foreign exchange rate risk. Our headquarters are located in the United States, where the majority of our general and administrative expenses and research and development costs are incurred in U.S. dollars. A portion of our research and development costs are incurred by our subsidiaries in Australia and Canada, whose functional currencies are the U.S. dollar but engage in transactions in Australian dollars and Canadian dollars, respectively. During each of the years ended December 31, 2022 and 2021, we recognized immaterial foreign currency transaction losses. These losses primarily related to unrealized and realized foreign currency gains and losses as a result of transactions entered into by our Australian and Canadian subsidiaries in currencies other than the U.S. dollar. These foreign currency transaction gains and losses were recorded in other expense, net in our consolidated statements of operations. We believe that a 10% change in the exchange rate between the U.S. dollar, Australian dollar and Canadian dollar would not have a material impact on our financial position or results of operations.

As we continue to grow our business, our results of operations and cash flows will be subject to fluctuations due to changes in foreign currency exchange rates, which could adversely impact our results of operations. To date, we have not entered into any foreign currency hedging contracts to mitigate our exposure to foreign currency exchange risk.

Item 8. Financial Statements and Supplementary Data.

All financial statements and supplementary data required to be filed hereunder are filed as listed under Item 15(a) of this Annual Report on Form 10-K and are incorporated herein by this reference.

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

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act 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 a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Based on the evaluation of our disclosure controls and procedures as of December 31, 2022, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at a reasonable assurance level as of the end of the period covered by this Annual Report on Form 10-K.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) for the Company. Our internal control over financial reporting is designed to provide reasonable assurances regarding the reliability of financial reporting and the preparation of our consolidated financial statements in accordance with U.S. GAAP and includes those policies and procedures that:

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

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

Our management, with the participation of its Chief Executive Officer and Chief Financial Officer, assessed our internal control over financial reporting as of December 31, 2022. Management based its assessment on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and concluded that our internal control over financial reporting was effective at the reasonable assurance level as of December 31, 2022.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for "emerging growth companies".

Changes in Internal Control over Financial Reporting

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the quarter ended December 31, 2022 that has materially affected, or is 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

Certain information required by Part III is omitted from this Annual Report on Form 10-K and is incorporated by reference from our definitive proxy statement relating to our 2023 annual meeting of stockholders, pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, also referred to in this Annual Report on Form 10-K as our 2023 Proxy Statement, which we expect to file with the SEC no later than April 28, 2023.

Item 10. Directors, Executive Officers and Corporate Governance.

Information required by this item with respect to our directors and executive officers and compliance with Section 16(a) of the Exchange Act will be included in our 2023 Proxy Statement and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this item regarding executive compensation will be included in our 2023 Proxy Statement 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 regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2023 Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item regarding certain relationships and related transactions and director independence will be included in our 2023 Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this item regarding principal accounting fees and services will be included in our 2023 Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are included in this Annual Report on Form 10-K:

1. The following Report and Consolidated Financial Statements of the Company are included in this Annual Report:

   Report of Independent Registered Public Accounting Firm

   Consolidated Balance Sheets

   Consolidated Statements of Operations and Comprehensive Loss

   Consolidated Statements of Stockholders' Equity

   Consolidated Statements of Cash Flows

   Notes to Consolidated Financial Statements

2. All financial schedules have been omitted because the required information is either presented in the consolidated financial statements or the notes thereto or is not applicable or required.

3. The exhibits required by Item 601 of Regulation S-K and Item 15(b) of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding the signature page of this Annual Report on Form 10-K. The exhibits listed in the Exhibit Index are incorporated by reference herein.

Item 16. Form 10-K Summary

Not Applicable.

AVROBIO, INC.
INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of AVROBIO, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of AVROBIO, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for the years then ended, 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 the years then ended, 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 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.

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 including 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 2018.
Boston, Massachusetts
March 23, 2023

AVROBIO, INC.
CONSOLIDATED BALANCE SHEETS
(amounts in thousands, except per share data)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 92,563	$ 189,567
Restricted cash	283	—
Prepaid expenses and other current assets	7,112	9,578
Total current assets	99,958	199,145
Operating lease assets	1,057	—
Property and equipment, net	2,894	4,126
Restricted cash, net of current portion	—	492
Other assets	40	74
Total assets	$ 103,949	$ 203,837
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 384	$ 3,486
Accrued expenses and other current liabilities	11,732	15,638
Operating lease liabilities	999	—
Deferred rent	—	262
Total current liabilities	13,115	19,386
Note payable, net of discount	15,276	14,945
Operating lease liabilities, net of current portion	188	—
Deferred rent, net of current portion	—	30
Total liabilities	28,579	34,361
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 10,000 shares authorized and no shares issued or outstanding as of December 31, 2022 and 2021	—	—
Common stock, $0.0001 par value; 150,000 shares authorized as of December 31, 2022 and 2021; 43,916 and 43,652 shares issued and outstanding as of December 31, 2022 and 2021, respectively	4	4
Additional paid-in capital	564,798	553,014
Accumulated deficit	(489,432)	(383,542)
Total stockholders' equity	75,370	169,476
Total liabilities and stockholders' equity	$ 103,949	$ 203,837

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

AVROBIO, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(amounts in thousands, except per share data)

	Year Ended December 31,	
	2022	2021
Operating expenses:		
Research and development	$ 72,186	$ 83,114
General and administrative	33,248	35,727
Total operating expenses	105,434	118,841
Loss from operations	(105,434)	(118,841)
Other expense:		
Interest (expense) income, net	(299)	(224)
Other expense, net	(157)	(61)
Total other (expense) income, net	(456)	(285)
Net loss and comprehensive loss	$ (105,890)	$ (119,126)
Net loss per share —basic and diluted	$ (2.42)	$ (2.78)
Weighted-average number of common shares outstanding—basic and diluted	43,739	42,854

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

AVROBIO, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(amounts in thousands)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount			
Balance as of December 31, 2020	41,569	$ 4	$ 518,756	$ (264,416)	$ 254,344
Vesting of restricted stock awards and units	1	—	—	—	—
Exercise of stock options	226	—	920	—	920
Issuance of common stock under ATM facility, net of offering costs of $47	1,829	—	14,550	—	14,550
Issuance of common stock under 2018 employee stock purchase plan	27	—	209	—	209
Stock-based compensation expense	—	—	18,579	—	18,579
Net loss	—	—	—	(119,126)	(119,126)
Balance as of December 31, 2021	43,652	4	553,014	(383,542)	169,476
Vesting of restricted stock units	1	—	—	—	—
Exercise of stock options	142	—	58	—	58
Issuance of common stock under 2018 employee stock purchase plan	121	—	204	—	204
Stock-based compensation expense	—	—	11,522	—	11,522
Net loss	—	—	—	(105,890)	(105,890)
Balance as of December 31, 2022	43,916	$ 4	$ 564,798	$ (489,432)	$ 75,370

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

AVROBIO, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(amounts in thousands)

	Year Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (105,890)	$ (119,126)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	11,522	18,579
Depreciation and amortization expense	1,440	1,399
Loss on disposal of property and equipment	59	—
Deferred rent expense	—	(223)
Non-cash interest expense	331	—
(Gain)/loss on impairment of leasehold improvements	86	—
(Gain)/loss on extinguishment of operating lease	(81)	—
Non-cash lease expense	2,726	—
Other	—	49
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	2,466	(2,018)
Other assets	34	362
Accounts payable	(3,102)	804
Current and non-current operating lease liabilities	(2,893)	—
Accrued expenses and other current liabilities	(3,906)	2,149
Net cash used in operating activities	(97,208)	(98,025)
Cash flows from investing activities:		
Purchases of property and equipment	(267)	(2,461)
Net cash used in investing activities	(267)	(2,461)
Cash flows from financing activities:		
Proceeds from issuance of common stock upon completion of public offerings, net of offering costs	—	(205)
Proceeds from long-term debt	—	15,000
Payments of issuance cost related to long-term debt	—	(103)
Proceeds from issuance of common stock under ATM facility, net of offering costs	—	14,550
Exercise of stock options	58	920
Proceeds from issuance of common stock under 2018 employee stock purchase plan	204	209
Net cash provided by financing activities	262	30,371
Net decrease in cash, cash equivalents and restricted cash	(97,213)	(70,115)
Cash, cash equivalents and restricted cash at beginning of period	190,059	260,174
Cash, cash equivalents and restricted cash at end of period	$ 92,846	$ 190,059
Supplemental Cash:		
Interest paid	$ 1,425	$ 98
Supplemental disclosure of non-cash investing and financing activities:		
Right of use asset obtained in exchange for operating lease liabilities	$ 4,319	$ —
Reconciliation of cash, cash equivalents and restricted cash reported within the consolidated balance sheets:		
Cash and cash equivalents, end of period	$ 92,563	$ 189,567
Restricted cash	283	492
Cash, cash equivalents and restricted cash, end of period	$ 92,846	$ 190,059

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

1. Nature of the Business

AVROBIO, Inc. (the "Company" or "AVROBIO") is a clinical-stage gene therapy company focused on developing potentially curative *ex vivo* lentiviral gene therapies to treat rare diseases following a single dose treatment regimen.

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, receiving 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. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and 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 the Financial Accounting Standards Board ("FASB") Accounting Standards Update ("ASU") 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern* (Subtopic 205-40), the Company has evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date that the consolidated financial statements are issued.

The Company has devoted substantially all of its efforts to research and development, business planning, acquiring operating assets, seeking protection for its technology and product candidates, and raising capital. Since inception, the Company has had recurring losses and has funded its operations through sales of preferred stock and common stock and a term loan facility. As of December 31, 2022, the Company had an accumulated deficit of $489,432.

The Company expects that its cash and cash equivalents of $92,563 as of December 31, 2022 may not be sufficient to fund operations for at least the next 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, and the Company will need to obtain additional funding. The Company expects to finance its operations through potential public or private equity financings, debt financings, collaboration agreements or other capital sources. The future viability of the Company is dependent on its ability to raise additional capital to finance its operations. 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

The accompanying 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 United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of AVROBIO, Inc. and its wholly owned subsidiaries. All intercompany transactions and balances have been eliminated in consolidation.

Segment Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the chief executive officer ("CEO"). The Company and the CEO view the Company's operations and manage its business as one operating segment. All material long-lived assets of the Company reside in the United States.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires that the Company make estimates and judgments that may affect the reported amounts of assets, liabilities and expenses and the related disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting periods. On an on-going basis, the Company evaluates its estimates, judgments and methodologies. The Company bases its estimates on historical experience and on various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results may differ from these estimates. Changes in estimates are reflected in reported results in the period in which they become known.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with original maturities of three months or less at acquisition to be cash equivalents. As of December 31, 2022 and 2021, cash and cash equivalents were primarily held in interest-bearing money market funds.

Concentrations of Credit Risk

The Company has no significant off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and restricted cash. Periodically, the Company maintains deposits in accredited financial institutions in excess of federally insured limits. The Company deposits its cash and cash equivalents in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

Fair Value Measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Fair value is defined as 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— Fair values are determined utilizing prices (unadjusted) in active markets for identical assets or liabilities that the Company has the ability to access.
- 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.

The carrying amounts of the Company's financial instruments, which include cash equivalents, accounts payable, and accrued expenses, approximated their fair values as of December 31, 2022 and 2021 due to the short-term nature of these instruments.

The Company has evaluated the estimated fair value of financial instruments using available market information. The use of different market assumptions, estimation methodologies, or both, could have a significant effect on the estimated fair value amounts. See Note 4 *"Fair Value of Financial Assets and Liabilities"* for further discussion.

Property and Equipment

Property and equipment are recorded at cost. Depreciation and amortization is calculated using the straight-line method over the following estimated useful lives of the assets:

	Estimated Useful Life
Laboratory and office equipment	5 years
Computer equipment	2 years
Leasehold improvements	Lesser of lease term or 10 years

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows. The Company did not record any impairment loss during the years ended December 31, 2022 and 2021.

Leases

Prior to January 1, 2022, the Company accounted for leases in accordance with FASB ASC 840, Leases. At lease inception, the Company determined if an arrangement was an operating or capital lease. For operating leases, the Company recognized rent expense, inclusive of rent escalations, on a straight-line basis over the lease term.

Effective on January 1, 2022, the Company accounts for leases in accordance with ASC Topic 842, Leases ("ASC 842"). Upon transition, the Company applied the package of practical expedients permitted under ASC 842 transition guidance to its entire lease portfolio at January 1, 2022. As a result, the Company was not required to reassess (i) whether any expired or existing contracts are or contain leases, (ii) the classification of any expired or existing leases, and (iii) initial direct costs for any existing leases. Furthermore, as a lessee the Company elected to combine lease and non-lease components together for the majority of its leases. As a result, for these applicable classes of underlying assets, the Company accounted for each separate lease component and the non-lease components associated with that lease component as a single lease component.

In accordance with ASC 842, the Company determines whether an arrangement is or contains a lease at inception. A contract is or contains a lease if the contract conveys the right to control the use of an identified asset for a period of time in exchange for consideration. The Company records leases at the lease commencement date, when control of the underlying asset is transferred from the lessor to the lessee, as operating or finance leases and records a right-of-use ("ROU") asset and a lease liability on the consolidated balance sheet for all leases with a lease term of greater than twelve months. The Company has elected to not recognize leases with a lease term of twelve months or less on the balance sheet and will recognize lease payments for such short-term leases as an expense on a straight-line basis.

The Company enters into contracts that contain both lease and non-lease components. Non-lease components may include items such as maintenance, utilities, or other operating costs. For leases of real estate, the Company combines the

lease and associated non-lease components in its lease arrangements as a single lease component. Variable costs, such as utilities or maintenance costs, are not included in the measurement of right-of-use assets and lease liabilities, but rather are expensed when the event determining the amount of variable consideration to be paid occurs.

Operating lease assets and liabilities are recognized at the lease commencement date based on the present value of the lease payments over the lease term using the discount rate implicit in the lease if readily determinable. If the rate implicit is not readily determinable, the Company utilizes its incremental borrowing rate based upon the available information at the lease commencement date. ROU assets are further adjusted for items such as initial direct costs, prepaid rent, or lease incentives. Operating lease payments are expensed using the straight-line method as an operating expense over the lease term. The Company's lease terms may include options to extend the lease when it is reasonably certain that the Company will exercise that option. Finance lease assets are amortized to depreciation expense using the straight-line method over the shorter of the useful life of the related asset or the lease term. Finance lease payments are bifurcated into (i) a portion that is recorded as interest expense and (ii) a portion that reduces the finance lease liability associated with the lease.

Comprehensive Income (Loss)

Comprehensive income (loss) is defined as the change in stockholders' equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive income (loss) includes net income (loss) as well as other changes in stockholders' equity (deficit) which includes certain changes in equity that are excluded from net income (loss). Comprehensive loss has been disclosed in the accompanying consolidated statements of operations and comprehensive loss and equals the Company's net loss for all periods presented.

Foreign Currency Translation

The functional currency of the Company's international operations in Canada and Australia is the U.S. dollar. Accordingly, all operating assets and liabilities of these international subsidiaries are remeasured into U.S. dollars using the exchange rates in effect at the balance sheet date or historical rates, as appropriate, while expenses are remeasured into U.S. dollars at the average rates in effect during the period. Any differences resulting from the remeasurement of assets, liabilities, and operations of the Canadian and Australian subsidiaries are recorded within other (expense) income, net in the consolidated statements of operations and comprehensive loss. During the years ended December 31, 2022 and 2021, the Company recorded foreign exchange losses of $92 and $61, respectively, in other expense in the consolidated statements of operations and comprehensive loss.

Research and Development Expenses

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries, stock-based compensation and benefits, facilities costs, depreciation, third-party license fees, and external costs of outside vendors engaged to conduct preclinical development activities and clinical trials as well as to manufacture research and development materials. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are recognized as an expense as the goods are delivered or the related services are performed or until it is no longer expected that the goods will be delivered or the services rendered.

The Company has entered into various research and development related contracts with parties both inside and outside of the United States. The payments related to these agreements are recorded as research and development expenses as incurred. The Company records accrued liabilities for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the 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.

Stock-Based Compensation

For stock-based awards issued to employees and members of the Company's board of directors (the "Board") for their services on the Board, the Company measures the estimated fair value of the stock-based award on the date of grant and recognizes compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. The Company issues stock-based awards with only service-based vesting conditions and records the

expense for these awards using the straight-line method. The Company has not issued any stock-based awards with performance- or market-based vesting conditions. The Company accounts for forfeitures as they occur.

The measurement date for non-employee awards is the later of the adoption date of ASU 2018-07, or the date of grant. For stock-based awards granted to nonemployees subject to graded vesting that only contain service conditions, the Company has elected to recognize stock-based compensation expense using the straight-line recognition method.

The Company classifies stock-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's cash compensation costs are classified.

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option pricing model. As there was no public market for its common stock prior to June 21, 2018, which was the first day of trading, and as the trading history of the Company's common stock was limited through December 31, 2022, the Company determined the volatility for awards granted based on an analysis of reported data for a group of guideline companies that issued options with substantially similar terms. The expected volatility has been determined using a weighted-average of the historical volatility measures of this group of guideline companies. The Company expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. The Company has not paid, and does not anticipate paying, cash dividends on its common stock; therefore, the expected dividend yield is assumed to be zero.

Income Taxes

Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements 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.

The Company accounts for uncertain tax positions recognized in the consolidated financial statements by prescribing a more-likely-than-not threshold for financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. 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.

Net Loss per Share

Basic net loss per share is computed by dividing net loss by the weighted-average number of shares of common stock outstanding during the period, without consideration of potential dilutive securities. Diluted net loss per share is computed by adjusting the weighted-average shares outstanding for the potential dilutive effects of common stock equivalents outstanding during the period calculated in accordance with the treasury stock method. For purposes of the diluted net loss per share calculation, stock options and restricted stock units are considered to be common stock equivalents but have been excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive for all periods presented. Therefore, basic and diluted net loss per share were the same for all periods presented.

Subsequent Event Considerations

The Company considers events or transactions that occur after the balance sheet date but prior to the issuance of the consolidated financial statements to provide additional evidence for certain estimates or to identify matters that require additional disclosure. Subsequent events have been evaluated as required. See Note 16.

Emerging Growth Company Status

The Company is an "emerging growth company," as defined in the Jumpstart Our Business Startups Act, or JOBS Act, and may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies. The Company may take advantage of these exemptions until the Company is no longer an "emerging growth company." Section 107 of the JOBS Act provides that an "emerging growth

company" 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, its consolidated financial statements may not be comparable to companies that comply with public company effective dates. The Company may take advantage of these exemptions up until the last day of the fiscal year following the fifth anniversary of an offering or such earlier time that it is no longer an "emerging growth company."

Recently Adopted Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases*, as subsequently amended (collectively, "ASC 842"), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors), and replaces the existing guidance in ASC 840, Leases.

As previously noted, the Company adopted ASC 842 with an effective date of January 1, 2022, using the modified retrospective transition approach which uses the effective date as the date of initial application. As a result, prior periods are presented in accordance with the previous guidance in ASC 840. The Company has elected to apply the package of practical expedients requiring no reassessment of whether any expired or existing contracts are or contain leases, the lease classification of any expired or existing leases, or the capitalization of initial direct costs for any existing leases.

Upon its adoption of ASC 842 on January 1, 2022, the Company recognized operating lease right-of-use assets of $1,301 and related operating lease liabilities of $1,593 on its balance sheet, and derecognized deferred rent liabilities of $292. The adoption of ASC 842 did not have a material impact on the Company's statements of operations and comprehensive loss or statements of cash flows.

In December 2019, the FASB issued ASU No. 2019-12, *Simplifying the Accounting for Income Taxes*, or ASU 2019-12. ASU 2019-12 eliminates certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. It also clarifies and simplifies other aspects of the accounting for income taxes. On January 1, 2022 the Company adopted this standard, which had no impact on its financial position or results of operations.

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, or ASU 2016-13. ASU 2016-13 requires that credit losses be reported as an allowance using an expected losses model, representing the entity's current estimate of credit losses expected to be incurred. The accounting guidance currently in effect is based on an incurred loss model. For available-for-sale debt securities with unrealized losses, this standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. ASU 2016-13 is effective for non-emerging growth companies ("EGCs") for fiscal years beginning December 15, 2019 and interim periods within those fiscal years, and will be effective for the Company for fiscal years beginning after December 15, 2022 and interim periods within those fiscal years, assuming the Company remains an EGC. Early adoption is permitted. The Company is currently evaluating the effects the adoption of ASU 2016-13 may have on its financial statements.

In November 2019, the FASB issued ASU 2019-11, "*Codification Improvements to Topic 326, Financial Instruments – Credit Losses*", or ASU 2019-11. ASU 2019-11 is an accounting pronouncement that amends ASU 2016-13, "Financial Instruments – Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments." The amendments update guidance on reporting credit losses for financial assets. These amendments affect loans, debt securities, trade receivables, net investments in leases, off balance sheet credit exposures, reinsurance receivables, and any other financial assets not excluded from the scope that have the contractual right to receive cash. The amendments in both ASU 2016-13 and ASU 2019-11 are effective for annual reporting periods beginning after December 15, 2019, including interim periods within those fiscal years. As a result of the Company having elected the extended transition period for complying with new or revised accounting standards pursuant to Section 107(b) of the JOBS Act, 2016-13 and ASU 2019-11 are effective for the Company for fiscal years beginning after December 15, 2022, and interim periods within those fiscal years. The Company is currently evaluating ASU 2016-13 and ASU 2019-11 and their impact on its consolidated financial statements and financial statement disclosures.

3. License Agreements

Agreement with The University of Manchester

On September 30, 2020, the Company entered into an agreement ("MPSII License Agreement") with The University of Manchester, England ("UoM"), whereby UoM granted to the Company an exclusive worldwide license under certain patent and other intellectual property rights, subject to certain retained rights, to develop, commercialize and sell an *ex vivo* lentiviral gene therapy for use in the treatment of Hunter syndrome, or mucopolysaccharidosis type II ("MPSII"). As consideration for the MPSII License Agreement, the Company agreed to pay UoM an upfront, one-time fee of $8,000, which was recognized as research and development expense during the year ended December 31, 2020.

As part of the agreement, the Company is obligated to make milestone payments of up to an aggregate of $80,000 upon the achievement of specified development and regulatory milestones, to pay royalties, on a product-by-product and country-by-country basis, of a mid-single digit percentage based on net sales of products licensed under the agreement and to pay a low double-digit percentage of any sublicense fees received by the Company. During the third quarter of 2022, a $2,000 milestone payment under the MPSII License Agreement became due following the date of regulatory approval of the CTA for the investigator-sponsored Phase 1/2 clinical trial sponsored by UoM. The next anticipated payment milestones under the MPSII License Agreement is $4,000 upon the dosing of the first patient in the investigator-sponsored Phase 1/2 clinical trial sponsored by UoM.

Unless terminated earlier, the agreement expires upon the later of 15 years from the effective date or the expiration of the last valid claim of the licensed patents, subject to certain surviving rights and obligations. UoM and the Company can each terminate the agreement in the event of the bankruptcy or insolvency of the other party, or a material breach by the other party and failure to cure such breach within a certain period of time. UoM has the right to terminate the agreement in the event of certain actions relating to challenge or opposition to the licensed intellectual property brought by the Company or its affiliates or sublicensees.

Concurrently with the MPSII License Agreement, the Company entered into a collaborative research funding agreement with UoM ("CRFA"). Under the CRFA, the Company has agreed to fund the budgeted costs of an investigator-sponsored Phase 1/2 clinical trial to be sponsored by UoM in connection with the development activities under the MPSII License Agreement, which are currently estimated to equal approximately £9,900 in the aggregate.

For the years ended December 31, 2022 and 2021, the Company recognized $2,346 and $1,437, respectively, of costs related to the CRFA.

Agreements with University Health Network ("UHN")

Fabry License Agreement—

On January 27, 2016, the Company entered into an agreement with UHN, pursuant to which UHN granted the Company an option to enter into an exclusive license under the UHN intellectual property related to Fabry disease in accordance with the pre-negotiated licensing terms. On November 4, 2016, the Company exercised its option and entered into a license agreement with UHN, pursuant to which UHN granted the Company an exclusive worldwide license under certain intellectual property rights and a non-exclusive worldwide license under certain know-how, in each case subject to certain retained rights, to develop, commercialize and sell products for use in the treatment of Fabry disease. In addition, for three years following the execution of the agreement, UHN granted the Company an exclusive option to obtain a license under certain improvements to the licensed intellectual property rights as well as an option to negotiate a license under certain other improvements.

Under this agreement, the Company paid an option fee of CAD$20, an upfront license fee of CAD$75, plus the annual license maintenance fee for the first year. Thereafter, the Company is also required to pay UHN future annual license maintenance fees until the first sale of a licensed product in certain markets. The Company is also obligated to make future milestone payments in an aggregate amount of up to CAD$2,450 upon the achievement of specified milestones as well as royalties on a country-by-country basis of a low to mid-single-digit percentage of annual net sales of licensed products and a lower single-digit royalty percentage in certain circumstances. Additionally, the Company has agreed to pay a low double-digit royalty percentage of all sublicensing revenue.

The agreement requires the Company to meet certain performance milestones within specified timeframes. UHN may terminate the agreement if the Company fails to meet these performance milestones despite using commercially reasonable efforts and the Company is unable to reach agreement with UHN on revised timeframes. The Company's royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration or termination of the last valid claim under the licensed intellectual property rights in such country, the tenth anniversary of the first commercial sale of such licensed product in such country and the expiration of any applicable regulatory exclusivity in such country.

Unless terminated earlier, the agreement expires upon the expiration of the Company's royalty obligation for all licensed products. UHN can terminate the agreement if the Company fails to make any payments within a specified period after receiving written notice of such failure, or in the event that the Company fails to obtain or maintain insurance. Either the Company or UHN may terminate the license agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time. The Company can voluntarily terminate the agreement with prior notice to UHN.

For the years ended December 31, 2022 and 2021, the Company recorded research and development expense related to this agreement with UHN of $161 and $209, respectively, which consists of reimbursable funded study trial costs and license maintenance fees. No milestone fees were incurred related to the Fabry license agreement in the years ended December 31, 2022 and 2021.

Interleukin 12 License Agreement—

On January 27, 2016, the Company entered into an exclusive license agreement with UHN, pursuant to which UHN granted the Company a license to certain patent rights for the commercial development, manufacture, distribution and use of any products or processes resulting from development of those patent rights related to Interleukin 12. Upon execution of this agreement, the Company paid an upfront license fee of CAD$264. In addition, as part of the initial consideration for the license, the Company issued to UHN 1,161,665 shares of the Company's common stock and agreed to pay UHN up to $2,000 upon the closing of an IPO if certain criteria are met. The fair value of the shares issued to UHN of $480 and the upfront fee was expensed upon the execution of the agreement. Upon the closing of the IPO in 2018, as the criteria were met, the Company paid UHN $2,000. The Company is also required to pay UHN future annual license maintenance fees of CAD$50 on each anniversary of the effective date of the license agreement prior to expiration or termination and potential future milestone payments of up to CAD$19,275 upon the achievement of specified clinical and regulatory milestones. The Company also agreed to pay UHN royalties of a low single-digit percentage of net sales of licensed products sold by the Company. If the Company grants any sublicense rights under the license agreement, the Company has agreed to pay UHN a low double-digit royalty percentage of any sublicense income received by the Company.

The agreement requires the Company to meet certain diligence requirements based upon specified milestones. The agreement expires on the later of the date the last patent rights expire in the last country or ten years from the date of first sale. UHN can terminate the agreement if the Company fails to make any payments within a specified period after receiving written notice of such failure, or in the event that the Company fails to obtain or maintain insurance. The Company can voluntarily terminate the agreement with prior notice to UHN. Either the Company or UHN may terminate the license agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time.

For the years ended December 31, 2022 and 2021, the Company recorded research and development expense related to this agreement with UHN of $39 for both periods, which consists of license maintenance fees. No milestone fees were incurred related to the Interleukin 12 license agreement in the years ended December 31, 2022 and 2021.

Agreement with BioMarin Pharmaceutical Inc. ("BioMarin")

On August 31, 2017, the Company entered into a license agreement with BioMarin, pursuant to which BioMarin granted the Company an exclusive worldwide license under certain intellectual property rights owned or controlled by BioMarin to develop, commercialize and sell products for use in the treatment of Pompe disease. The license agreement was amended in February 2018 and again in January 2020 to, among things, provide that BioMarin would supply the Company with certain technology materials. As consideration for this agreement, the Company paid an upfront license fee of $500 in cash and issued 233,765 shares of Series B Preferred Stock to BioMarin at the time of the Company's Series B Preferred Stock financing in January 2018. The Company is also obligated to make future milestone payments of up to $13,000 upon the achievement of certain specified milestones and agreed to pay BioMarin royalties of a low single-digit percentage of net sales of licensed products sold by the Company or its affiliates covered by patent rights in a relevant country. No expenses related to the license were recorded for the years ended December 31, 2022 and 2021.

Unless terminated earlier, the agreement expires upon the expiration of the Company's royalty obligation for all licensed products throughout the world. BioMarin and the Company can terminate the agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time. The Company may terminate the agreement at will upon written notice to BioMarin. BioMarin has the right to terminate the agreement upon the Company's bankruptcy or insolvency, or in the event of any challenge or opposition to the licensed patent rights or related actions brought by the Company or its affiliates or sublicensees, or if the Company, its affiliates or sublicensees knowingly assist a third-party in challenging or otherwise opposing the licensed patent rights, except as required under a court order or subpoena.

Agreement with Papillon Therapeutics, Inc. (previously GenStem Therapeutics, Inc.)

On October 2, 2017, the Company entered into a license agreement with GenStem, pursuant to which GenStem granted the Company an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights owned or controlled by GenStem to develop, commercialize and sell products for use in the treatment of cystinosis. Under this agreement, the Company paid an upfront license fee of $1,000 and is required to make payments upon completion of certain milestones up to an aggregate of $16,000. The Company also agreed to pay GenStem a tiered mid to high single-digit royalty percentage on annual net sales of licensed products as well as a low double-digit percentage of sublicense income received from certain third-party licensees. The Company's royalty obligation expires on a licensed product-by-licensed product and country-by-country basis on the eleventh anniversary of the first commercial sale of such licensed product in such country or the expiration of the last valid claim under the licensed patent rights covering such licensed product in such country, whichever is later. Unless terminated earlier, the agreement expires upon the expiration of the Company's royalty obligation for all licensed products throughout the world. GenStem and the Company can terminate the agreement in the event of a material breach by the other party and failure to cure such breach within a certain period of time. The Company may terminate the agreement at will upon the specified prior written notice to GenStem. In October 2021, the Company received notice that the license agreement with GenStem had been assigned to Papillon.

No expenses related to the license were recorded for the years ended December 31, 2022 and 2021.

Agreement with Lund University Rights Holders

On November 17, 2016, the Company entered into a license agreement with affiliates of Lund University, along with certain other relevant rights holders that may be added from time to time, pursuant to which such rights holders granted to the Company an exclusive worldwide license, subject to certain retained rights, under certain intellectual property rights to develop, commercialize and sell products in any and all uses relevant to Gaucher disease. As consideration for the license, the Company is required to make payments in connection with the achievement of certain milestones up to an aggregate of $550. The agreement expires on the latest of (i) the twentieth anniversary of the end of a certain research project the Company is funding pursuant to an agreement with Lund University, (ii) the expiration of the term of any patent filed on the licensed rights that covers a licensed product, (iii) the expiration of any applicable marketing exclusivity right and (iv) such time that neither the Company nor any sublicensees, partners or contractors are commercializing a licensed product. Either the Company or the rights holders acting together may terminate the license agreement if the other such party commits a material breach and fails to cure such breach within a certain period of time, or if the other party enters into liquidation, becomes insolvent, or enters into composition or statutory reorganization proceedings. No expenses related to the license were recorded for the years ended December 31, 2022 and 2021.

4. Fair Value of Financial Assets and Liabilities

The following table presents information about the Company's financial assets and liabilities measured at fair value on a recurring basis and indicates the level of the fair value hierarchy utilized to determine such fair values as of December 31, 2022 and 2021:

	Fair Value Measurements as of December 31, 2022			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents—money market funds	$ 91,095	$ —	$ —	$ 91,095
	$ 91,095	$ —	$ —	$ 91,095

	Fair Value Measurements as of December 31, 2021			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents—money market funds	$ 189,332	$ —	$ —	$ 189,332
	$ 189,332	$ —	$ —	$ 189,332

During the years ended December 31, 2022 and 2021, there were no transfers between levels.

5. Supplemental Balance Sheet Information

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following:

	December 31,	
	2022	2021
Prepaid research and development expenses	$ 4,509	$ 4,496
Tax incentive refund, net of reserve	269	2,697
Prepaid insurance	999	112
Prepaid compensation benefits	327	575
Other current assets	1,008	1,698
Prepaid expenses and other current assets	$ 7,112	$ 9,578

Property and Equipment, Net

Property and equipment, net consisted of the following:

	December 31,	
	2022	2021
Laboratory and office equipment	$ 5,967	$ 6,162
Leasehold improvements	629	1,635
Computer equipment	102	149
	6,698	7,946
Less: Accumulated depreciation and amortization	(3,804)	(3,820)
Property and equipment, net	$ 2,894	$ 4,126

Depreciation and amortization expense for the years ended December 31, 2022 and 2021 was $1,440 and $1,399, respectively.

Restricted Cash

As of December 31, 2022 and 2021, the Company had restricted cash as presented in the table below, which consists of cash used to secure letters of credit for the benefit of the landlord in connection with the Company's lease agreements. The cash will be restricted until the termination or modification of the lease arrangement.

	December 31,	
	2022	2021
Restricted cash	$ 283	$ —
Restricted cash, net of current portion	—	492

Accrued Expenses

Accrued expenses consisted of the following:

	December 31,	
	2022	2021
Research and development expenses	$ 6,122	$ 8,882
Compensation and benefit costs	4,175	5,579
Consulting and professional fees	1,224	999
Other liabilities	211	178
	$ 11,732	$ 15,638

6. Leases

On January 12, 2018, the Company entered into a lease agreement for office space located in Cambridge, Massachusetts. The lease agreement was set to expire in January 2023 and was terminated early in September 2022. The annual lease payments were subject to a 3% increase each year. The Company received a tenant incentive allowance of $842 in 2018. In accordance with the lease agreement, the Company was required to maintain a security deposit of $209, which was recorded in restricted cash as of December 31, 2021.

On August 31, 2018, the Company entered into a sublease agreement for lab space located in Cambridge Massachusetts, United States, which was set to expire in October 2020. On June 9, 2020, the Company amended the terms of the sublease, which was set to expire in April 2022. Effective January 1, 2022, the Company amended the terms of the sublease, to extend the term through April 2023. In July 2022, the company moved our corporate headquarters to our subleased space in this location. Effective January 24, 2023, the Company amended the terms of the sublease, which is now set to expire in April 2024. The annual lease payments are subject to a 5% increase each year. In accordance with the lease agreement, the Company is required to maintain a security deposit of $283, which was recorded in restricted cash as of December 31, 2022 and 2021.

On June 1, 2020, the Company entered into a lease agreement for office space located in Toronto, Ontario, Canada, which is set to expire in June 2025. The annual lease payments are fixed for years 1 and 2, and then subject to a 6.67% increase for years 3 through 5. In accordance with the lease agreement, the Company is required to maintain a security deposit of CAD$27, which was recorded in other long-term assets as of December 31, 2022 and 2021. In October 2022, the Company entered into a sublease agreement to sublease this space. The term of the sublease agreement commenced on October 1, 2022 and expires on June 29, 2025.

The following table summarizes the effect of lease costs in the Company's consolidated statement of operations and comprehensive loss:

	Year ended December 31, 2022
Operating lease costs	$ 2,994
Sublease income	(23)
Total lease costs	$ 2,971

During the year ended December 31, 2022 the Company made cash payments for operating leases of $3,167.

As of December 31, 2022, future minimum payments of operating lease liabilities are as follows (in thousands):

	As of December 31, 2022
2023	$ 1,007
2024	138
2025	69
2026	—
2027	—
Thereafter	—
Total lease payments	$ 1,214
Less: interest	(53)
Plus: FX gain/loss	26
Present value of lease liabilities	$ 1,187

As of December 31, 2022, the weighted average remaining lease term was 0.9 years and the weighted average incremental borrowing rate used to determine the operating lease liability was 10.58%.

Future minimum payments required under the leases as of December 31, 2021 presented in accordance with ASC 840, the relevant accounting standard at that time (in thousands):

Year Ending December 31,	
2022	$ 1,297
2023	208
2024	147
2025	73
Total	$ 1,725

Rent expense during the year ended December 31, 2021 was $2,648.

7. Note Payable

On November 2, 2021 (the "Closing Date"), the Company entered into a Loan and Security Agreement (the "Loan Agreement") with Silicon Valley Bank pursuant to which a term loan in an aggregate principal amount of up to $50,000 (the "Term Loan Facility") is available to the Company in three tranches, subject to certain terms and conditions. The first tranche of $15,000 was advanced to the Company on the Closing Date. Subject to the terms and conditions of the Loan Agreement, the first tranche allows the Company to borrow an additional $15,000 through October 31, 2023. Upon satisfaction of certain milestones, the second and third tranches are available under the Term Loan Facility which allows the Company to borrow an additional amount up to $10,000 in each tranche through October 31, 2023. Additionally, the Company may seek to borrow up to an additional $15,000 at the sole discretion of the lender through the term of the Loan Agreement. The Loan Agreement matures on October 1, 2026 (the "Maturity Date"). The Company is required to pay an end of term fee ("End of Term Charge") equal to 9.00% of the aggregate principal amount of the Term Loan advances upon repayment.

Advances under the Term Loan Facility will bear interest at a rate equal to the greater of either (i) the Prime Rate (as reported in The Wall Street Journal) plus 4.85%, and (ii) 8.10%. The Company will make interest only payments through November 1, 2024. Following the interest only period, the Company will repay the principal balance and interest of the advances in equal monthly installments through October 1, 2026.

The Company may prepay advances under the Loan Agreement, in whole or in part, at any time subject to a prepayment charge (the "Prepayment Premium") equal to: (a) 1.50% of amounts so prepaid, if such prepayment occurs during the first year following the Closing Date; (b) 1.00% of the amount so prepaid, if such prepayment occurs during the second year following the Closing Date, and (c) 0.00% of the amount so prepaid, if such prepayment occurs after the second year following the Closing Date.

Upon prepayment or repayment of all or any of the term loans under the Term Loan Facility, the Company will pay (in addition to any Prepayment Premium) an end of term charge of 9.0% of the aggregate funded amount under the Term Loan Facility.

The Term Loan Facility is secured by substantially all of the Company's assets, other than the Company's intellectual property. The Company has agreed to not pledge or secure its intellectual property to others. The Term Loan Facility is subject to certain terms and conditions that would be considered an Event of Default, including any material adverse change to the Company.

The End of Term Charge is recorded as a debt discount with an initial carrying balance of $1,350. During the year ended December 31, 2021 the Company recognized $103 of debt issuance costs related to legal expenses that has been included in the debt discount balance. The debt discount costs are being accreted to the principal amount of debt and being amortized from the date of issuance through the Maturity Date to interest expense using the effective-interest rate method. The effective interest rate of the outstanding debt under the Loan Agreement is approximately 15.00%.

As of December 31, 2022 and 2021 the carrying value of the note payable consists of the following:

	December 31,	
	2022	2021
Note payable, including End of Term Charge	$ 16,350	$ 16,350
Debt discount, net of accretion	(1,074)	(1,405)
Note payable, net of discount, long-term	$ 15,276	$ 14,945

As of December 31, 2022, the future principal payments due under the arrangement, excluding interest and the end of term charge, are as follows:

Year Ending December 31,	Principle
2023	$ —
2024	1,875
2025	7,500
2026	5,625
Total	$ 15,000

During the year ended December 31, 2022, the Company recognized $1,808 of interest expense related to the Loan Agreement, which is reflected in other (expense) income, net on the consolidated statements of operations and comprehensive loss. During year ended December 31, 2021, the Company recognized $203 of interest expense related to the Loan Agreement.

8. Common Stock

As of December 31, 2022 and 2021, the authorized capital stock of the Company included 150,000,000 shares of common stock, $0.0001 par value, and 10,000,000 shares of undesignated preferred stock. As of December 31, 2022 and 2021, no undesignated shares of preferred stock were outstanding.

In accordance to the Fourth Amended and Restated Certificate of Incorporation, the holders of the common stock shall have the exclusive right to vote for the election of directors of the Company and on all other matters requiring stockholder action, each outstanding share entitling the holder thereof to one vote on each matter properly submitted to the stockholders of the Company for their vote; provided, however, that, except as otherwise required by law, holders of common stock, as such, shall not be entitled to vote on any amendment to any amendment to a certificate of designations of any series of undesignated preferred stock that alters or changes the powers, preferences, rights or other terms of one or more outstanding series of undesignated preferred stock if the holders of such affected series of undesignated preferred stock are entitled to vote, either separately or together with the holders of one or more other such series, on such amendment pursuant to a certificate of designations of any series of undesignated preferred stock.

Through December 31, 2022, no cash dividends have been declared or paid.

Public Offerings

In July 2019, the Company closed an underwritten public offering of 7,475,000 shares of its common stock at a public offering price of $18.50 per share (the "July 2019 Follow-on Offering"), which included 975,000 shares of the Company's common stock resulting from the full exercise of the underwriters' option to purchase additional shares at the public offering price, less underwriting discounts and commissions. The net proceeds to the Company from the July 2019 Follow-on Offering, after deducting underwriting discounts and commissions and other offering expenses payable by the Company, were $129,464.

In February 2020, the Company closed an underwritten public offering of 4,350,000 shares of its common stock at a public offering price of $23.00 per share (the "February 2020 Follow-on Offering"). The net proceeds to the Company from the February 2020 Follow-on Offering, after deducting underwriting discounts and commissions and other offering expenses payable by the Company, were $93,627.

In June 2020, the Company sold an aggregate of 384,140 shares of common stock under its 2019 "at-the-market" facility (the "2019 ATM Facility") for net proceeds, after deducting commissions and other offering expenses payable by the Company, of $8,130.

In November 2020, the Company closed an underwritten public offering of 5,000,000 shares of its common stock at a public offering price of $15.00 per share (the "November 2020 Follow-on Offering"). The net proceeds to the Company from the November 2020 Follow-on Offering, after deducting underwriting discounts and commissions and other offering expenses payable by the Company, were $70,221.

In May 2021, the Company sold an aggregate of 1,829,268 shares of common stock under the 2019 ATM Facility for net proceeds, after deducting commissions and other offering expenses payable by the Company, of $14,550. As of December 31, 2022, approximately $26,549 of common stock remained available for future issuance under the 2019 ATM Facility.

Common Stock Reserved for Future Issuance

As of December 31, 2022 and 2021, the Company has reserved the following shares of common stock for future issuance:

	December 31,	
	2022	2021
Shares reserved for exercise of outstanding stock options	9,423,271	7,423,777
Shares reserved for vesting of restricted stock units	940,392	599,850
Shares reserved for issuance under the 2018 Stock Option and Incentive Plan	5,005,295	2,583,736
Shares reserved for issuance under the 2018 Employee Stock Purchase Plan	1,467,026	1,151,010
Shares reserved for issuance under the 2019 Inducement Plan	786,656	412,686
Shares reserved for issuance under the 2020 Inducement Plan	1,637,000	1,637,000
Total shares of authorized common stock reserved for future issuance	19,259,640	13,808,059

9. Stock-Based Compensation

Amended and Restated 2015 Stock Option and Grant Plan

The Company's Amended and Restated 2015 Stock Option and Grant Plan, (the "2015 Plan") provides for the Company to issue restricted stock awards and restricted stock units, or to grant incentive stock options or non-statutory stock options. Incentive stock options may be granted only to the Company's employees including officers and members of the Board who are also employees. Restricted stock awards and restricted stock units and non- statutory stock options may be granted to employees, members of the Board, outside advisors, and consultants of the Company.

The total number of common shares that may be issued under the 2015 Plan was 2,008,564 shares. Following the IPO, no further grants have been made under 2015 plan.

Shares that expire, are terminated, surrendered or cancelled under the 2015 Plan without having been fully exercised will be available for future awards under the 2018 Plan (as defined below). In addition, 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.

The 2015 Plan is administered by the Board. Equity awards granted to employees and members of the Board typically vest over four years.

2018 Stock Option and Incentive Plan

The Company's 2018 Stock Option and Incentive Plan (the "2018 Plan") was adopted by the Board on June 1, 2018 and approved by stockholders on June 7, 2018 and became effective upon the effectiveness of the Company's Registration Statement on Form S-1. The 2018 Plan replaced the 2015 Plan as the Board determined not to make additional awards under the 2015 Plan following the pricing of the Company's IPO. The 2018 Plan allows the Board, compensation committee or other designated committee to make equity-based and cash-based incentive awards to its officers, employees, directors and other key persons (including consultants).

The Company initially reserved 616,300 shares of its common stock for the issuance of awards under the 2018 Plan. The 2018 Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2019, by 4% of the outstanding number of shares of our common stock on the immediately preceding December 31, or such lesser number of shares as determined by its Board or compensation committee (the "Plan Evergreen"). This number is subject to adjustment in the event of a stock split, stock dividend or other change in its capitalization.

On April 16, 2020, the Board adopted an amendment to the 2018 Plan (the "Amendment"), to (i) increase the number of shares of common stock currently reserved for issuance under the 2018 Plan by 3,300,000 shares and (ii) automatically terminate the 2018 Plan's annual increase (or "evergreen") provision after January 2022. The Amendment was approved by the Board on June 4, 2020 and the Company's stockholders on June 4, 2020.

The number of shares of common stock available for future grant under the 2018 Plan was 5,005,295 as of December 31, 2022, which does not include the shares added to the 2018 Plan reserve on January 1, 2022 as a result of the Plan Evergreen for the year ended December 31, 2022.

During the years ended December 31, 2022 and 2021, the Company granted options to purchase 5,369,650 and, 4,253,232 shares, respectively, of common stock to employees, nonemployees and members of the Board.

2018 Employee Stock Purchase Plan

The Company's 2018 Employee Stock Purchase Plan (the "ESPP") was adopted by the Board on June 1, 2018 and approved by stockholders on June 7, 2018 and became effective upon the effectiveness of the Company's Registration Statement on Form S-1. The ESPP is intended to qualify as an "employee stock purchase plan" within the meaning of Section 423(b) of the Code. The ESPP initially reserves and authorizes the issuance of up to a total of 223,200 shares of common stock to participating employees. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2019 and each January 1 thereafter through January 1, 2028, by the least of (i) 1% of the outstanding number of shares of our common stock on the immediately preceding December 31; (ii) 1,115,700 shares or (iii) such number of shares as determined by the ESPP administrator (the "ESPP Evergreen"). The

number of shares reserved under the ESPP is subject to adjustment in the event of a stock split, stock dividend or other change in our capitalization.

During the years ended December 31, 2022 and 2021, the Company issued 120,947 and 27,580 shares, respectively of common stock. The total number of shares of common stock available for future grant was 1,467,026 as of December 31, 2022, which does not include the shares added to the ESPP reserve on January 1, 2023 as a result of the ESPP Evergreen for the year ended December 31, 2022.

2019 Inducement Plan

The Company's 2019 Inducement Plan (the "2019 Plan") was adopted by the Board on December 11, 2019. The purpose of the 2019 Plan is to allow the Company to grant equity awards to new employees as inducements material to such new employee's acceptance of employment with the Company. The Company intends that the shares underlying the 2019 Plan be reserved for persons to whom the Company may issue securities without stockholder approval as an inducement pursuant to Rule 5635(c)(4) of the Nasdaq marketplace rules.

The Company initially reserved 1,800,000 shares of its common stock for the issuance of awards under the 2019 Plan.

The number of shares of common stock available for future grant under the 2019 Plan was 786,656 as of December 31, 2022.

2020 Inducement Plan

The Company's 2020 Inducement Plan (the "2020 Plan") was adopted by the Board on December 9, 2020. The purpose of the 2020 Plan is to allow the Company to grant equity awards to new employees as inducements material to such new employee's acceptance of employment with the Company. The Company intends that the shares underlying the 2020 Plan be reserved for persons to whom the Company may issue securities without stockholder approval as an inducement pursuant to Rule 5635(c)(4) of the Nasdaq marketplace rules.

The Company initially reserved 1,700,000 shares of its common stock for the issuance of awards under the 2020 Plan.

The number of shares of common stock available for future grant under the 2020 Plan was 1,637,000 as of December 31, 2022.

Stock Option Valuation

The assumptions that the Company used to determine the grant-date fair value of stock options granted to employees and members of the Board were as follows, presented on a weighted-average basis:

	Year Ended December 31,	
	2022	2021
Expected option life (years)	5.98	6.06
Risk-free interest rate	2.47%	0.80%
Expected volatility	80.43%	81.22%
Expected dividend yield	—%	—%

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

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding as of December 31, 2021	7,423,777	$ 13.54	6.79	$ 1,469
Granted	5,369,650	$ 1.43		
Exercised	(142,013)	$ 0.41		
Cancelled or forfeited	(3,228,143)	$ 12.31		
Outstanding as of December 31, 2022	9,423,271	$ 7.26	8.14	$ 22
Exercisable as of December 31, 2022	3,068,082	$ 13.11	6.15	$ 22

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the underlying stock options and the estimated fair value of the Company's common stock for those stock options that had exercise prices lower than the estimated fair value of the Company's common stock.

The aggregate intrinsic value of options exercised during the years ended December 31, 2022 and 2021 was $50 and $1,826, respectively.

The weighted-average grant-date fair value of the Company's stock options granted during the years ended December 31, 2022 and 2021 was $0.99 and $8.70, respectively.

Restricted Common Stock

The Company has granted restricted common stock (or restricted stock awards) with time-based vesting conditions to certain employees of the Company. The purchase price of the restricted stock awards are determined by the Board. Unvested shares of restricted stock awards may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award. The Company has the option to repurchase the restricted stock awards at the original purchase price if the grantee terminates its working relationship with the Company prior to the vesting date. There were no unvested restricted stock awards as of December 31, 2022.

Restricted stock units

Restricted stock units represent an unsecured promise to grant at no cost a set number of shares of common stock upon vesting. With respect to restricted stock units, recipients are not entitled to cash dividends and have no voting rights during the vesting period.

The following table summarizes the Company's restricted stock award and restricted stock unit activity for the year ended December 31, 2022:

	Number of Shares	Weighted-Average Grant Date Fair Value
Issued and unvested as of December 31, 2021	599,850	$ 9.64
Granted	920,168	1.56
Vested	(575)	15.65
Forfeited, cancelled or expired	(579,051)	6.56
Issued and unvested as of December 31, 2022	940,392	$ 3.62

The total fair value of restricted stock awards and restricted stock units vested during the years ended December 31, 2022 and 2021 was $9 and $5, respectively.

Stock-Based Compensation

Stock-based compensation expense was allocated as follows:

	Year Ended December 31,	
	2022	2021
Research and development	$ 2,785	$ 6,996
General and administrative	8,737	11,583
Total stock-based compensation expense	$ 11,522	$ 18,579

As of December 31, 2022, total unrecognized compensation cost related to unvested stock-based awards was $18,719, which is expected to be recognized over a weighted-average period of 2.3 years.

10. 401(k) Savings Plan

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code. Eligible employees may make pretax contributions to the 401(k) Plan up to statutory limits. At the election of the Board, the Company may elect to match employee contributions. Currently, the Company makes matching contributions at a rate of 50% of the first 8% of employee contributions. The Company recorded $599 and $593 of expenses related to its 401(k) match for the years ended December 31, 2022 and 2021, respectively.

11. Commitments and Contingencies

Lease Agreements

Refer to Note 6 "Leases" for discussion of the commitments associated with the Company's lease portfolio.

Other Funding Commitments

As of December 31, 2022, the Company had several ongoing clinical and non-clinical studies for its various pipeline programs. The Company enters into contracts in the normal course of business with contract research organizations and clinical sites for the conduct of clinical trials, professional consultants for expert advice and other vendors for clinical supply manufacturing or other services. These contracts are generally cancellable, with notice, at the Company's option and do not have significant cancellation penalties.

Guarantees

The Company enters into certain agreements with other parties in the ordinary course of business that contain indemnification provisions. These typically include agreements with directors and officers, business partners, contractors, landlords and clinical sites. Under these provisions, the Company generally indemnifies and holds harmless the indemnified party for losses suffered or incurred by the indemnified party as a result of the Company's activities. These indemnification provisions generally survive termination of the underlying agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification provisions is unlimited. However, to date the Company has not incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. As a result, the estimated fair value of these obligations is minimal.

Litigation

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company was not subject to any material legal proceedings during the years ended December 31, 2022 and 2021, and to the best of its knowledge, no material legal proceedings are currently pending or threatened.

Other

The Company is also party to various agreements, principally relating to licensed technology, that require future payments relating to milestones not met as of December 31, 2022 and 2021, or royalties on future sales of specified products.

No milestone or royalty payments under these agreements are expected to be payable in the immediate future. See Note 3 *"Licenses Agreements"* for discussion of these arrangements.

The Company enters into standard indemnification agreements in the ordinary course of business. Pursuant to the agreements, the Company agrees to indemnify, hold harmless, and to reimburse the indemnified party for losses suffered or incurred by the indemnified party, generally the Company's business partners, in connection with any U.S. patent or any copyright or other intellectual property infringement claim by any third-party with respect to the Company's products. 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 is unlimited. The Company has never incurred costs to defend lawsuits or settle claims related to these indemnification agreements.

12. Income Taxes

For the years ended December 31, 2022 and 2021, the Company did not record a current or deferred income tax expense or (benefit) due to current and historical losses incurred by the Company. The Company's operations are predominantly based in the United States and the Company's foreign subsidiaries generated *de minimis* losses for the years ended December 31, 2022 and 2021.

A reconciliation of income tax expense (benefit) computed at the statutory federal income tax rate to the Company's effective tax rate as reflected in the consolidated financial statements is as follows:

	Year Ended December 31,	
	2022	2021
Federal income tax expense at statutory rate	21.0%	21.0%
State income taxes, net of federal benefit	5.2%	6.0%
Permanent differences	-1.2%	-1.2%
Foreign rate differential	0.0%	0.1%
Research and development tax credits	0.8%	2.0%
Change in valuation allowance	-25.8%	-27.9%
Provision to Return	0.0%	0.0%
Effective income tax rate	0.0%	0.0%

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 are comprised of the following:

	December 31,	
	2022	2021
Deferred tax assets:		
U.S., foreign and state net operating loss carryforwards	$ 91,416	$ 84,102
Research and development credits	8,471	7,821
Capitalized start up and organizational costs	23	26
Equity based compensation	3,610	3,926
Licensing agreements	3,929	3,749
Section 174 R&D Capitalization	16,307	—
Lease Liability	227	—
Accruals and other	1,032	1,376
Total deferred tax assets	125,015	101,000
Valuation allowance	(124,695)	(100,893)
Net deferred tax assets	$ 320	$ 107
Deferred tax liabilities:		
Property and equipment	$ (102)	$ (107)
ROU Asset	(218)	—
Total deferred tax liabilities	$ —	$ —

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. As of December 31, 2022 and 2021 based on the Company's history of operating losses, the Company has concluded that it is not more likely than not that the benefit of its deferred tax assets will be realized. Accordingly, the Company has provided a full valuation allowance for deferred tax assets as of December 31, 2022 and 2021. The valuation allowance increased by $23,802 and $30,401 during the years ended December 31, 2022 and 2021, respectively, due primarily to net operating losses generated.

As of December 31, 2022 and 2021, the Company had U.S. federal net operating loss carryforwards of $340,350 and $312,967, respectively, that may be available to offset future income tax liabilities. The U.S. federal tax operating loss carryforwards of approximately $17,743 will expire at various dates through 2037. Approximately $322,607 of the U.S. federal tax operating losses can be carried forward indefinitely. As of December 31, 2022 and 2021, the Company also had U.S. state net operating loss carryforwards of $316,668 and $290,500, respectively, which may be available to offset future taxable income. These losses expire at various dates beginning in 2041.

As of December 31, 2022 and 2021, the Company had federal research and development tax credit carryforwards of $6,824 and $6,234, respectively. Included in the $6,824 of federal tax credit carryforwards are $2,027 of orphan drug credits. Through the year ended December 31, 2020 the Company qualifies for, and has elected to, apply part of its federal research credits against its payroll tax liability in accordance with certain provisions of the Internal Revenue Code. The amount applied towards the Company's payroll tax liability is capped at $250 per year. The federal research credits generated in excess of the $250 cap are able to be carried forward for 20 years. As of December 31, 2022 and 2021, the Company had state research and development tax credit carryforwards of approximately $2,084 and $1,959, respectively, available to reduce future tax liabilities which expire at various dates beginning in 2037. For all years through December 31, 2022, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards.

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 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 percentage points, 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 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 completed numerous financings since its inception, which may have resulted in a change in control as defined by Sections 382 and 383 of the Internal Revenue Code, or could result in a change in control in the future.

The Company files income tax returns in the United States, Australia and Canada, and in several states. The foreign, federal and state income tax returns are generally subject to tax examinations for the tax years ended December 31, 2016 through December 31, 2020. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by foreign tax authorities, the Internal Revenue Service, or state tax authorities to the extent utilized in a future period.

13. Net Loss per Share

For purposes of the diluted net loss per share calculation, stock options, unvested restricted stock awards and unvested restricted stock units are considered to be common stock equivalents but have been excluded from the calculation of diluted net loss per share, as their effect would be anti-dilutive for all periods presented. Therefore, 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 potentially dilutive common stock equivalents, presented based on amounts outstanding at each period end, were excluded from the computation of diluted net loss per share attributable to common stockholders for the periods indicated:

	Year Ended December 31,	
	2022	2021
Options to purchase common stock	9,423,271	7,423,777
Restricted stock awards and units	940,392	599,850

14. Related Party Transactions

UHN

In connection with the Company's entry into a license agreement with UHN on January 27, 2016, the Company issued UHN 1,161,665 shares of its common stock. Upon the closing of the IPO in 2018, as UHN's fully-diluted percentage ownership of the Company was reduced within a range of specified percentages, the Company was obligated to pay UHN an amount of $2,000, which was paid in July 2018. For the years ended December 31, 2022 and 2021, the Company recognized $200 and $248, respectively, of research and development expense related to the license agreements with UHN. Refer to Note 3 *"License Agreements"* for additional information regarding the UHN license agreements.

Others

For the years ended December 31, 2022 and 2021, the Company recorded expenses of $3,200 and $1,523, respectively, related to a sublease to rent lab space, provided by an entity affiliated with a member of the board.

15. Restructuring

In January 2022, the Company announced the deprioritization of AVR-RD-01, its investigational gene therapy program for Fabry disease. This decision was made due to several factors, including new clinical data showing variable engraftment patterns from the five most recently dosed patients in the Company's Phase 2 clinical trial of AVR-RD-01 for the treatment of Fabry disease, which the Company refers to as the FAB-GT clinical trial. The emergence of such new data would have significantly extended the program's development timeline. That development, coupled with an increasingly challenging market and regulatory environment for Fabry disease, were among the primary factors leading to the Company's deprioritization of its Fabry program. As a result of the deprioritization, the Company has stopped enrollment of its Phase 2 FAB-GT clinical trial and has shifted focus to its other pipeline programs.

In connection with the deprioritization of AVR-RD-01 noted above, in January 2022, the Company approved changes to the Company's organization as well as a broader operational cost reduction plan. As part of this plan, the Company approved a reduction in the Company's workforce by approximately 23% across different areas and functions in the Company (the "Workforce Reduction").

Under the Workforce Reduction, the Company recognized total restructuring expenses for the year ended December 31, 2022 of $1,369, which are included within Research and development and General and administrative expenses. No restructuring expenses were incurred for the year ended December 31, 2021. These one-time employee termination benefits are related to affected employees, who were offered separation benefits, including severance payments. During the year ended December 31, 2022 approximately $1,369 of these payments were made. There are no remaining payments accrued at December 31, 2022.

16. Subsequent Events

On March 10, 2023, Silicon Valley Bank, based in Santa Clara, California, was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation ("FDIC") as receiver. On March 12, 2023, the U.S. Treasury, Federal Reserve, and FDIC announced that depositors with Silicon Valley Bank or its successor bridge bank (collectively, "SVB") will have access to all of their money starting March 13, 2023. Our agreement with SVB currently requires substantially all of our cash and cash equivalents to be deposited with SVB, and we historically have relied primarily on SVB for commercial banking services. We are pursuing actions to make alternative banking arrangements, including opening deposit accounts at one or more other financial institutions. SVB has agreed to waive covenants related to maintaining our deposits at SVB for a period of 30 days, during which time we have agreed to obtain an Account Control Agreement ("ACA") for all accounts held outside of SVB. The Company has concluded that it is probable that it will obtain the ACA for all accounts held outside of SVB prior to the expiration of the 30-day waiver period to be compliant with its covenants.

EXHIBIT NO.	EXHIBIT INDEX
3.1	Fourth Amended and Restated Certificate of Incorporation of the Registrant (filed as Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed on June 25, 2018 (File No. 001-38537) and incorporated herein by reference)
3.2	Certificate of Change of Registered Agent and/or Registered Office of the Registrant (filed as Exhibit 3.2 to the Registrant's Quarterly Report on Form 10-Q filed on November 5, 2020 (File No. 001-38537) and incorporated herein by reference)
3.3	Amended and Restated By-laws (filed as Exhibit 3.2 to the Registrant's Current Report on Form 8-K filed on June 25, 2018 (File No. 001-38537) and incorporated herein by reference)
4.1	Form of Specimen Common Stock Certificate (filed as Exhibit 4.1 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
4.2	Second Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, dated January 9, 2018 (filed as Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
4.3	Description of Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934, as amended (filed as Exhibit 4.3 to the to the Registrant's Annual Report on Form 10-K filed on March 16, 2020 (File No. 001-38537) and incorporated herein by reference)
10.1#	2015 Amended and Restated Stock Option and Grant Plan, as amended, and forms of award agreements thereunder (filed as Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.2#	2018 Stock Option and Incentive Plan and forms of award agreements thereunder (filed as Exhibit 10.2 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.3#	First Amendment to the AVROBIO, Inc. 2018 Stock Option and Incentive Plan (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on June 9, 2020 (File No. 001-38537) and incorporated herein by reference)
10.4#	Second Amendment to the AVROBIO, Inc. 2018 Stock Option and Incentive Plan (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on June 10, 2022 (File No. 001-38537) and incorporated herein by reference)
10.5#	Senior Executive Cash Incentive Bonus Plan (filed as Exhibit 10.3 to the Registrant's Second Amendment to the Registration Statement on form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.6#	Form of Indemnification Agreement (filed as Exhibit 10.4 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.7†	Exclusive License Agreement, by and between the Registrant and University Health Network, dated November 4, 2016, as amended (filed as Exhibit 10.5 to the Registrant's First Amendment to the Registration Statement on Form S-1 filed on June 1, 2018 (File No. 333-225213) and incorporated herein by reference)
10.8†	License Agreement, by and between the Registrant and BioMarin Pharmaceutical Inc., dated August 31, 2017 (filed as Exhibit 10.6 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.9††	Amendment No. 1 to License Agreement, by and between the Registrant and BioMarin Pharmaceutical Inc., dated February 21, 2018 (filed as Exhibit 10.7 to the to the Registrant's Annual Report on Form 10-K filed on March 16, 2020 (File No. 001-38537) and incorporated herein by reference)
10.10††	Amendment No. 2 to License Agreement, by and between the Registrant and BioMarin Pharmaceutical Inc., dated January 7, 2020 (filed as Exhibit 10.8 to the to the Registrant's Annual Report on Form 10-K filed on March 16, 2020 (File No. 001-38537) and incorporated herein by reference)

EXHIBIT NO.	EXHIBIT INDEX
10.11†	Exclusive License Agreement, by and among the Registrant, Stefan Karlsson and Maria Dahl, dated January 30, 2017 (filed as Exhibit 10.7 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.12†	License Agreement, by and between the Registrant and GenStem Therapeutics, Inc., dated October 2, 2017 (filed as Exhibit 10.8 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)
10.13#	Amended and Restated Employment Agreement, by and between the Registrant and Geoff MacKay, effective as of June 25, 2018 (filed as Exhibit 10.9 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.14#	Amendment to Employment Agreement, by and between the Registrant and Geoff MacKay, dated April 5, 2021 (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 13, 2021 (File No. 001-38537) and incorporated herein by reference
10.15#	Employment Agreement, by and between the Registrant and Erik Ostrowski, dated December 17, 2018 (filed as Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed on December 21, 2018 (File No. 001-38537) and incorporated herein by reference)
10.16#	Amendment to Employment Agreement, by and between the Registrant and Erik Ostrowski, dated April 5, 2021 (filed as Exhibit 10.2 to the Registrant's Quarterly Report on Form 10-Q filed on May 13, 2021 (File No. 001-38537) and incorporated herein by reference
10.17#	Employment Agreement, by and between the Registrant and Steven Avruch, dated December 17, 2018 (filed as Exhibit 10.13 to the Registrant's Annual Report on Form 10-K filed on March 25, 2019 (File No. 001-38537) and incorporated herein by reference)
10.18#	Amendment to Employment Agreement, by and between the Registrant and Steven Avruch, dated April 5, 2021 (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on May 13, 2021 (File No. 001-38537) and incorporated herein by reference
10.19#	Employment Agreement, by and between the Registrant and Deanna Petersen, dated September 1, 2018 (filed as Exhibit 10.16 to the Registrant's Annual Report on Form 10-K filed on March 16, 2020 (File No. 001-38537) and incorporated herein by reference)
10.20#	Amendment to Employment Agreement, by and between the Registrant and Deanna Petersen, dated April 5, 2021 (filed as Exhibit 10.6 to the Registrant's Quarterly Report on Form 10-Q filed on May 13, 2021 (File No. 001-38537) and incorporated herein by reference)
10.21#	Employment Agreement, by and between the Registrant and Chris Mason, dated September 1, 2018 (filed as Exhibit 10.19 to the Registrant's Annual Report on Form 10-K filed on March 18, 2021 (File No. 001-38537) and incorporated herein by reference)
10.22#	Amendment to Employment Agreement, by and between the Registrant and Chris Mason, dated April 5, 2021 (filed as Exhibit 10.5 to the Registrant's Quarterly Report on Form 10-Q filed on May 13, 2021 (File No. 001-38537) and incorporated herein by reference)
10.23#	Amendment No. 2 to Employment Agreement, by and between the Registrant and Chris Mason, dated April 25, 2022 (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on May 10, 2022 (File No. 001-38537) and incorporated herein by reference)
10.24#	Employment Agreement, by and between the Registrant and Essra Ridha, dated October 6, 2021 (filed as Exhibit 10.22 to the Registrant's Annual Report on Form 10-K filed on March 17, 2022 (File No. 001-38537) and incorporated herein by reference)
10.25#	2018 Employee Stock Purchase Plan (filed as Exhibit 10.14 to the Registrant's Second Amendment to the Registration Statement on Form S-1 filed on June 11, 2018 (File No. 333-225213) and incorporated herein by reference)
10.26	Lease Agreement, dated as of January 12, 2018, by and between the Registrant and ARE-MA Region No. 59, LLC (filed as Exhibit 10.12 to the Registrant's Registration Statement on Form S-1 filed on May 25, 2018 (File No. 333-225213) and incorporated herein by reference)

EXHIBIT NO.	EXHIBIT INDEX
10.27#	2019 Inducement Plan and form of award agreement thereunder (filed as Exhibit 99.1 to the Registrant's Registration Statement on Form S-8 filed on December 20, 2019 (File No. 333-235643) and incorporated herein by reference)
10.28#	Form of 2019 Inducement Stock Option Award (filed as Exhibit 99.1 to the Registrant's Registration Statement on Form S-8 filed on March 25, 2019 (File No. 333-230493) and incorporated herein by reference)
10.29#	2020 Inducement Plan and form of award agreement thereunder (filed as Exhibit 10.25 to the Registrant's Annual Report on Form 10-K filed on March 18, 2021 (File No. 001-38537) and incorporated herein by reference)
10.30	Loan and Security Agreement, dated November 2, 2021, by and among the Registrant, the lenders party thereto from time to time and Silicon Valley Bank, as administrative agent and collateral agent (filed as Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q filed on November 4, 2021 (File No. 001-38537) and incorporated herein by reference)
10.31††	Amended and Restated Master Services Agreement, by and between the Registrant and Miltenyi Biotec, Inc., dated November 20, 2021 (filed as Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q filed on August 9, 2022 (File No. 001-38537) and incorporated herein by reference)
21.1	Subsidiaries of the Registrant
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm
24.1	Power of Attorney (included on the signature page)
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 and 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	Interactive Data Files pursuant to Rule 405 of Regulation S-T formatted in Inline Extensible Business Reporting Language ("Inline XBRL")
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101.*)

† Confidential treatment has been granted for portions of this Exhibit pursuant to Rule 406 promulgated under the Securities Act of 1933, as amended.
†† Portions of this exhibit have been omitted because they are both (i) not material and (ii) would likely cause competitive harm to the registrant if publicly disclosed.
# Indicates a management contract or any compensatory plan, contract or arrangement.
* Indicates the exhibit is being furnished, not filed, with this report.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on the 23rd day of March, 2023.

AVROBIO, INC.

By: /s/ Geoff Mackay
Geoff MacKay
President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Geoff MacKay and Erik Ostrowski, and each of them, his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this report, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or either of them, or their or his substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Geoff MacKay Geoff MacKay	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 23, 2023
/s/ Erik Ostrowski Erik Ostrowski	Chief Financial Officer *(Principal Financial Officer and Principal Accounting Officer)*	March 23, 2023
/s/ Bruce Booth Bruce Booth, D.Phil.	Chairman of the Board of Directors	March 23, 2023
/s/ Ian T. Clark Ian T. Clark	Director	March 23, 2023
/s/ Gail Farfel, Ph.D. Gail Farfel	Director	March 23, 2023
/s/ Phillip B. Donenberg Phillip B. Donenberg	Director	March 23, 2023
/s/ Annalisa Jenkins Annalisa Jenkins, M.B.B.S., F.R.C.P	Director	March 23, 2023
/s/ Christopher Paige Christopher Paige, Ph.D.	Director	March 23, 2023
/s/ Philip J. Vickers Philip J. Vickers, Ph.D.	Director	March 23, 2023

EXECUTIVE MANAGEMENT

Erik Ostrowski, MBA
President, Interim CEO & Chief Financial Officer

Steven Avruch, JD
Chief Legal Officer

Azadeh Golipour, PhD
Chief Technology Officer

Deanna Petersen, MBA
Chief Business Officer

Essra Ridha, MD, MRCP, FFPM
Chief Medical Officer

BOARD OF DIRECTORS

Bruce Booth, DPhil
Chairman
Partner, Atlas Venture

Ian Clark
Director, biotechnology companies,
Former CEO, Genentech

Phillip Donenberg
Advisor and Director, biotechnology companies,
Former Senior Vice President & Chief Financial Officer,
Jaguar Gene Therapy, LLC

Gail Farfel, PhD
Chief Executive Officer, ProMIS Neurosciences, Inc.

Annalisa Jenkins, MBBS, FRCP
Advisor and Director, biotechnology companies,
Former CEO, Dimension Therapeutics

Christopher Paige, PhD, FCAHS
Senior Scientist Emeritus, University Health Network,
Professor, University of Toronto

Philip Vickers, PhD
Director, biotechnology companies,
Former CEO, Faze Medicines

STOCKHOLDER INFORMATION

ANNUAL MEETING
June 6, 2023 | 9:00 AM EDT
The meeting will be held virtually at
www.proxydocs.com/AVRO

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Cambridge, MA 02142

AUDITORS
Ernst & Young LLP
200 Clarendon Street Boston, MA 02116

EXTERNAL CORPORATE COUNSEL
Goodwin Procter LLP
100 Nothern Avenue Boston, MA 02210

TRANSFER AGENT
Computershare Trust Company NA
250 Royall Street Canton, MA 02021
Phone: 800.942.5909

STOCK LISTING
NASDAQ: **AVRO**

AVROBIO

Our passion for our work is driven by the families we aim to serve

They inspire us daily as we work to deliver freedom from a lifetime of genetic disease

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