

**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, 2020

OR

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

For the transition period from \_\_\_\_\_ to \_\_\_\_\_

Commission file number: 001-39319

**GENERATION BIO CO.**

(Exact name of registrant as specified in its charter)

Delaware  
(State or other jurisdiction of  
incorporation or organization)  
  
301 Binney Street  
Cambridge, Massachusetts  
(Address of principal executive offices)

81-4301284  
(I.R.S. Employer  
Identification Number)

02142  
(Zip Code)

(617) 655-7500

(Registrant's telephone number, including area code)

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, \$0.0001 Par Value	GBIO	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	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input checked="" type="checkbox"/>
		Emerging growth company	<input checked="" type="checkbox"/>

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.

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 Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant's Common Stock as of June 30, 2020, the last business day of the registrant's most recently completed second fiscal quarter, was approximately \$646.2 million (based on the last reported sale price on the Nasdaq Global Select Market as of such date). For this computation, the registrant has excluded the market value of all shares of Common Stock reported as beneficially owned by its executive officer and directors; such exclusion shall not be deemed to constitute an admission that any such person is an affiliate of the registrant.

As of February 28, 2021, there were 56,427,399 shares of the registrant's Common Stock, \$0.0001 par value per share, outstanding.

**DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's Proxy Statement for its 2021 Annual Meeting of Stockholders, which the registrant intends to file with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2020, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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## CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or this Annual Report, of Generation Bio Co. contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that involve substantial risks and uncertainties. All statements, other than statements of historical fact, contained in this Annual Report, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would,” or the negative of these words or other similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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

- the initiation, timing, progress and results of our research and development programs and preclinical studies and clinical trials;
- our estimates regarding expenses, future revenue, capital requirements, need for additional financing and the period over which we believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital expenditure requirements;
- our plans to develop and, if approved, subsequently commercialize any product candidates we may develop;
- the timing of and our ability to submit applications for, obtain and maintain regulatory approvals for any product candidates we may develop;
- the potential advantages of our non-viral gene therapy platform;
- our estimates regarding the potential addressable patient populations for our programs;
- the impact of the COVID-19 pandemic and our response to the pandemic;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our expectations regarding our ability to obtain and maintain intellectual property protection;
- our intellectual property position;
- our ability to identify additional products, product candidates or technologies with significant commercial potential that are consistent with our commercial objectives;
- the impact of government laws and regulations;
- our competitive position and expectations regarding developments and projections relating to our competitors and any competing therapies that are or become available;
- developments and expectations regarding developments and projections relating to our competitors and our industry;
- our ability to maintain and establish collaborations or obtain additional funding; and
- our expectations regarding the time during which we will be an emerging growth company under the Jumpstart Our Business Startup Act of 2012.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and stockholders should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report, particularly in the “Risk Factors Summary” and “Risk Factors” sections, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Moreover, we operate in

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a competitive and rapidly changing environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures, or investments we may make or enter into.

Stockholders should read this Annual Report and the documents that we file with the Securities and Exchange Commission with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report are made as of the date of this Annual Report, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

Except where the context otherwise requires or where otherwise indicated, the terms “we,” “us,” “our,” “our company,” “the company,” and “our business” in this Annual Report refer to Generation Bio Co. and its consolidated subsidiary.

## RISK FACTOR SUMMARY

We are providing the following summary of the risk factors contained in this Annual Report to enhance the readability and accessibility of our risk factor disclosures. We encourage stockholders to carefully review the full risk factors contained in this Annual Report in their entirety for additional information regarding the material factors that make an investment in our securities speculative or risky. These risks and uncertainties include, but are not limited to, the following:

- We are very early in our development efforts. We have not identified any product candidates for IND-enabling studies or clinical development. As a result, it will be many years before we commercialize a product candidate, if ever. If we are unable to identify and advance product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them, or experience significant delays in doing so, our business will be materially harmed;
- We will need substantial additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts;
- Our limited operating history may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability;
- Our non-viral gene therapy platform is based on novel technologies that are unproven, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all;
- We may encounter substantial delays in commencement, enrollment or completion of our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, any of which could prevent us from commercializing any product candidates we may develop on a timely basis, if at all;
- If any product candidates we may develop cause undesirable side effects or have other unexpected adverse properties, such side effects or properties could delay or prevent regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval;
- The outcome of preclinical studies may not be predictive of later preclinical studies or clinical trials;
- Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate we may develop, or the approval may be for a more narrow indication than we expect;
- The manufacture of genetic medicine products is complex and difficult and is subject to a number of scientific and technical risks, some of which are common to the manufacture of drugs and biologics and others of which are unique to the manufacture of gene therapies. We could experience manufacturing problems that result in delays in our development or commercialization programs;
- We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, research, preclinical and clinical testing, and these third parties may not perform satisfactorily;
- If we fail to comply with our obligations under our existing license agreements, or under any future intellectual property licenses, or otherwise experience disruptions to our business relationships with our current or any future licensors, we could lose intellectual property rights that are important to our business;
- If we are unable to obtain and maintain patent protection for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize any product candidates we may develop and technology may be adversely affected; and
- The ongoing COVID-19 pandemic and its effects on our business and operations are uncertain. We and our contract development and manufacturing organizations and contract research organizations

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experienced a temporary reduction in the capacity to undertake research scale production and to execute some preclinical studies, and we may face disruptions in the future that affect our ability to initiate and complete preclinical studies and to procure items that are essential for our research and development activities.

## PART I

### ITEM 1. BUSINESS

#### Overview

We are an innovative genetic medicines company creating a new class of gene therapy utilizing our proprietary non-viral gene therapy platform to provide durable, redosable treatments for millions of patients living with rare and prevalent diseases. Our non-viral gene therapy platform incorporates our high-capacity DNA construct called closed-ended DNA, or ceDNA; our cell-targeted lipid nanoparticle delivery system, or ctLNP; and our established, scalable capsid-free manufacturing process. Using our approach, we are developing novel gene therapies to provide targeted delivery of genetic payloads that include large and multiple genes to a range of tissues across a broad array of diseases. We are also engineering our gene therapies to be redosable, which may enable individualized patient titration to reach the desired level of therapeutic expression and to maintain efficacy throughout a patient's life.

We are advancing a broad and expansive portfolio of programs, including programs for rare and prevalent diseases of the liver and retina. We are focused on diseases with significant unmet need for which our non-viral gene therapy platform may substantially improve clinical efficacy relative to current gene therapy approaches. We are initially prioritizing rare monogenic diseases of the liver and retina, which are diseases that result from mutations in a single gene, that have well-established biomarkers and clear clinical and regulatory pathways.

We plan to expand our portfolio to include rare and prevalent diseases of the skeletal muscle, the central nervous system, or CNS, and oncology by developing discrete ctLNPs, each engineered to reach a different tissue. In parallel, we are developing the constructs and manufacturing capacity to rapidly advance new disease programs in a tissue or area once human proof of concept is established.

We believe our non-viral gene therapy platform may allow patients to produce antibody therapies from their own cells for years at a time from a single dose, and plan to advance antibody gene therapy programs across multiple therapeutic areas. The combination of the expected multi-year durability of a single dose of ceDNA, tissue-specific delivery and manufacturing capacity may provide dosing for millions of patients living with prevalent diseases.

While we are currently a preclinical stage company and are early in our development efforts, we believe that our new class of gene therapy has the potential to reach previously untreatable or under-treated patients and address new indications, including those with large patient populations, thereby unlocking the full potential of genetic medicine. Specifically, we believe that our platform has the potential to provide durable and redosable therapies that will enable:

- expanded patient access, including the ability to treat children;
- delivery of large genetic payload, including large and multiple genes;
- native gene regulation;
- targeted delivery to a range of tissues;
- large-scale cost-effective production;
- treatment for millions of patients across the globe; and
- a sustainable payer model.

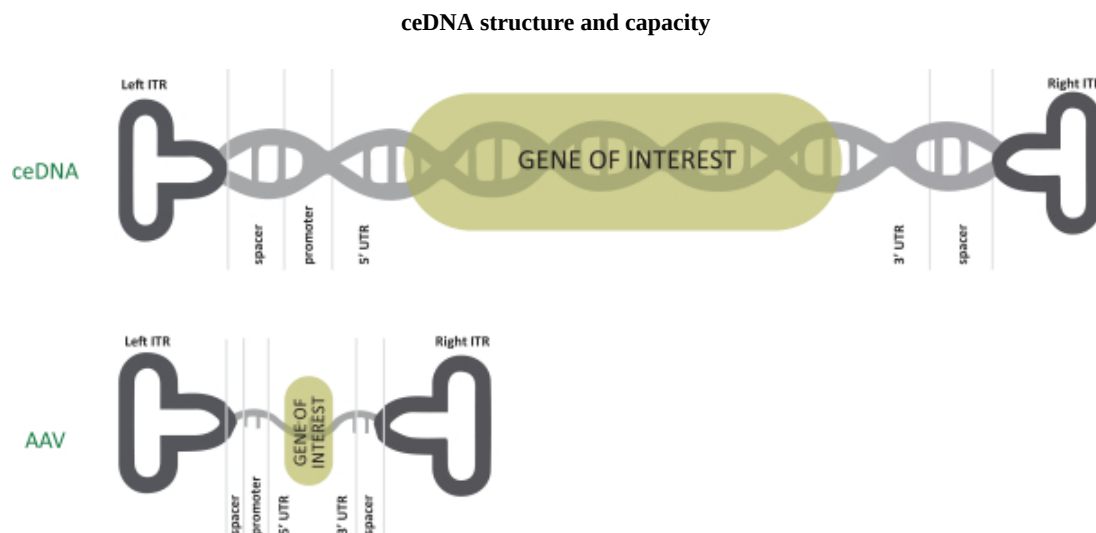
#### ***Our non-viral gene therapy platform***

Our non-viral gene therapy platform is comprised of three essential components: our high-capacity ceDNA construct, which can accommodate large or multiple genes as well as native regulatory elements; our ctLNP delivery system, which enables highly specific delivery of ceDNA to a range of tissues; and our established, scalable capsid-free manufacturing process, which uses a cost-effective biologics infrastructure that has the

potential to reach patients with rare diseases and to expand access to patients with prevalent diseases, requiring millions of doses, on a sustainable basis.

### ceDNA

Our high-capacity ceDNA is an engineered, double-stranded, linear, covalently closed-ended DNA construct that includes the gene of interest and associated regulatory sequences. We have produced ceDNA constructs of 12 kilobases, or kb, which have almost three times the 4.7 kb capacity of adeno-associated virus, or AAV, gene therapy approaches. The structure and relative size of ceDNA as compared to AAV is shown in the figure below. We believe ceDNA can deliver a significant majority of the human coding sequences known to be relevant for the treatment of diseases that result from mutations in a single gene or in multiple genes. ceDNA may address many diseases, including prevalent diseases and diseases requiring more than one type of genetic correction that are beyond the scope of current gene therapy. This capacity can also accommodate native or engineered regulatory elements, potentially enabling a powerful new dimension of gene therapy that responds to the body's own signals.



### ctLNP

Our ctLNP delivery system builds upon clinically validated lipid nanoparticles, or LNPs, and is designed to allow for repeat dosing of a genetic payload without stimulating an immune response, such as antibody production. We have taken a significant step beyond current LNP technology by adding a biological targeting molecule, called a ligand, on the surface of our LNPs to direct their biodistribution to specific tissues. Different targeting ligands may enable our ctLNPs to actively target specific cell receptors in the liver, retina, skeletal muscle, CNS and tumors. In addition, our ctLNP delivery system may confer the advantages of predictable behavior across species, minimal off-target effects and a foundational platform approach that unlocks the ability to target the widest possible spectrum of diseases with our therapies.

### Manufacturing process

Our established, scalable manufacturing employs a proprietary, capsid-free process and utilizes standard biologics infrastructure, unlike traditional viral gene therapy manufacturing. Viral gene therapy relies on a protein capsid for therapeutic delivery of a viral vector, and as a result, the manufacturing process for viral gene therapies requires the production of protein capsids, which limit process scalability and consistency. Our capsid-



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free manufacturing process is an efficient and reproducible process that includes rigorous, industrial-scale purification that consistently yields greater than 99% pure ceDNA.

We have established a current Good Manufacturing Practices, or cGMP, -ready process at the 200-liter scale, which we have successfully transferred to external contract development and manufacturing organizations, or CDMOs, for production of clinical supply.

Our ability to conduct this manufacturing process at the 200-liter scale with high product quality suggests that further scaling to thousands of liters per batch is feasible using standard biological production equipment and engineering methods.

We believe the combination of the expected multi-year durability of a single dose of ceDNA, tissue-specific delivery and manufacturing capacity may provide dosing for millions of patients living with prevalent diseases. We also believe these features will allow the cost of production for our non-viral gene therapy platform to compare favorably to the cost of production of current biologic products.

**Our portfolio**

We are advancing a broad and expansive portfolio of programs, including programs for rare and prevalent diseases of the liver and retina. We are focused on diseases with significant unmet need for which our non-viral gene therapy platform may substantially improve clinical efficacy relative to current gene therapy approaches. We are initially prioritizing rare monogenic diseases of the liver and retina that have well-established biomarkers and clear clinical and regulatory pathways.

We plan to expand our portfolio to include rare and prevalent diseases of the skeletal muscle, the CNS and oncology by developing discrete ctLNPs, each engineered to reach a different tissue. In parallel, we are developing the constructs and manufacturing capacity to rapidly advance new disease programs in a tissue or area once human proof of concept is established. As shown in the figure below, our most advanced liver disease programs are in hemophilia A and phenylketonuria, or PKU, which are in the preclinical stage of development, and our most advanced retina disease programs are in Leber’s Congenital Amaurosis, or LCA10, and Stargardt disease, which are in the lead optimization stage of development. In the lead optimization stage, we are seeking to identify ceDNA constructs that provide disease relevant expression in an animal model, and in the preclinical stage of development, we are conducting additional *in vivo* studies to identify development candidates and are assessing these candidates in investigational new drug, or IND, -enabling studies.



In December 2019, we held an Initial Targeted Engagement for Regulatory Advice on CBER Products, or INTERACT, meeting with the FDA’s Office of Tissues and Advanced Therapies, or OTAT, to introduce our platform and align on the manufacturing and analytical control strategy to support clinical development in PKU.

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We expect to select the development candidate for each of our hemophilia A and PKU programs and to initiate IND-enabling studies for these programs in 2021, followed by IND applications for these programs in 2022. We anticipate submitting IND applications for additional programs in 2023 and beyond.

Our programs in the liver and retina as well as in our expansion opportunities are wholly owned by us. For the majority of our programs, we have designed and produced ceDNAs that have shown expression *in vitro* and/or disease correction *in vivo*.

### **Our strategy**

Our goal is to become an industry leader in the field of genetic medicines, advancing our non-viral gene therapy platform to discover, develop, manufacture and globally commercialize a new class of gene therapy that is durable, redosable and specifically delivered to a range of tissues for the treatment of diseases caused by single, large or multiple gene defects. We aim to provide sustainable, life-long treatment for millions of patients living with rare and prevalent diseases.

Our research and development efforts have resulted in numerous innovations and breakthroughs across every aspect of our platform. We own or exclusively license patent applications in 41 patent application families covering our programs and technology, including our ceDNA platform, ctLNP delivery system and our manufacturing processes, and have taken other steps to protect our proprietary position with respect to these innovations and breakthroughs. Our wholly owned intellectual property, combined with the background technology we have licensed from the National Institutes of Health, or NIH, and the University of Massachusetts Medical School, or UMass, and Voyager Therapeutics, Inc., or Voyager, based on our co-founder's prior work, supports the leading position of our non-viral gene therapy platform and provides a strong foundation for its continued advancement.

### **Our culture and team**

We have established a highly collaborative, patient-first culture that fuels our innovation. Our team learns, develops and thrives as a community guided by four core values: together we are thoughtful, inclusive, courageous and all-in for our mission to create solutions for patients and their families.

Our management team has extensive collective expertise in human genetics, rare disease drug development and commercialization and the manufacture and delivery of nucleic acid therapeutics. Geoff McDonough, M.D., our President and Chief Executive Officer, brings over 20 years of leadership experience with innovative life science companies across strategy, corporate and business development, program management and global drug development and launches. Douglas Kerr, M.D., Ph.D., M.B.A., our Chief Medical Officer, is a pioneer in the development of rare neuroscience programs with more than 15 years of industry experience. Matthew Norkunas, M.D., M.B.A., our Chief Financial Officer, brings his combined financial and medical expertise and depth of experience in both biotechnology company and investor settings. Matthew Stanton, Ph.D., our Chief Scientific Officer, is an expert in nucleic acid therapeutic development and delivery platforms with over 20 years of experience across pharmaceutical and biotechnology companies. Tracy Zimmermann, Ph.D., our Chief Development Officer, has 20 years of industry experience advancing novel nucleic acid based therapeutics into development.

In the aggregate, our management team has been involved in the filing of over 25 INDs and contributed to the development of 20 approved products, including Biogen's SPINRAZA (nusinersen); Sanofi Genzyme's FABRAZYME (agalsidase beta), ALDURAZYME (laronidase) and MYOZYME (alglucosidase alfa); Sobi and Biogen's ELOCTATE and ALPROLIX; Vertex Pharmaceuticals Inc.'s KALYDECO (ivacaftor), ORKAMBI (lumacaftor/ivacaftor) and SYMDEKO (tezacaftor/ivacaftor); Alnylam's ONPATTRO (patisiran) and GIVLAARI (givosiran); and Moderna, Inc.'s mRNA-1944, an investigational therapy for the chikungunya virus.

Our organization is comprised of more than 100 talented individuals with significant experience across discovery, preclinical research, manufacturing and clinical development. We have also established scientific and

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clinical advisory boards comprised of leading experts in the fields of human genetics, rare disease drug discovery and development and global regulatory engagement, who share our mission of providing sustainable, life-long treatment for millions of patients living with rare and prevalent diseases.

### **The genetic medicines industry**

#### ***Background***

The human genome is made up of approximately 25,000 genes, which act as a set of instructions to influence and determine every aspect of how the body functions. A genetic disease is caused by a change, or a mutation, in an individual's DNA sequence. Genetic diseases can be caused by a mutation in a single gene, known as a monogenic disorder, or by mutations in multiple genes, known as a multifactorial inheritance disorder. Current estimates suggest that there are more than 10,000 monogenic diseases. Many of these are rare, affecting hundreds or thousands of patients worldwide, such as hemophilia A or PKU. There are an even greater number of prevalent diseases whose genetics are multifactorial, affecting millions of people on a global scale, such as many types of metabolic disease and cancer.

Genetic medicines are designed to correct disease-causing dysfunction at the genetic level and utilize recombinant nucleic acids to regulate, repair, replace, add or delete a genetic sequence to achieve the desired therapeutic effect. Viral gene therapy, gene editing and messenger RNA, or mRNA, are genetic medicine modalities that specifically aim to replace the function of disease-causing genes by either inserting a gene, modifying the DNA, or inserting mRNA into a patient's cell.

Early gene therapy clinical trials in the 1990's used adenovirus to deliver genetic material. However, developers have moved away from using adenoviruses because they can trigger a strong immune reaction and their effect is short lived. Another form of viral gene therapy uses retroviral vectors, including lentiviral vectors, to incorporate DNA directly into a cell's chromosome upon infection, typically through *ex vivo* delivery. In *ex vivo* delivery, genetic modification of isolated patient or donor cells are conducted outside of the patient and then re-introduced to the patient. As an integrating virus, these vectors pose additional safety risks, and create the potential for disrupting genes or activating cancer-causing genes. In addition, *ex vivo* delivery poses a significant operational challenge and higher cost relative to *in vivo* therapies. As a result, AAV has become a preferred viral vector for gene therapy.

Significant progress has been made in the field of genetic medicine over the last decade with products approved in viral gene therapy, and several gene editing and mRNA programs in clinical development. While we expect that there will be further advancements in these modalities, each possesses distinct clinical and commercial limitations due to known safety, efficacy, therapeutic delivery and manufacturing scale challenges.

#### ***Current and emerging genetic medicines and their limitations***

##### ***Viral gene therapy***

Viral gene therapy, in which viral vectors are employed to deliver therapeutic genes to defective cells or tissues, has made significant progress in the past decade. The most advanced system for systemic administration is AAV gene therapy, which has demonstrated durable transduction of cells in several organ systems, with long-lasting expression in non-dividing cells. Several AAV gene therapy products have been approved, including LUXTURN A (voretigene neparvovec-rzyl) for the treatment of the rare inherited blindness disorder biallelic RPE65 mutation-associated retinal dystrophy and ZOLGENSMA (onasemnogene abeparvovec-xioi) for spinal muscular atrophy, or SMA.

However, current AAV gene therapy has demonstrated limitations, including:

- *Single dose administration only*: Following a single dose of AAV, antibodies are induced against the AAV capsid, the protein shell of the virus used for delivery. Because of these antibodies, AAV can only be dosed once, and it is typically dosed at the upper end of its therapeutic index to maximize potential efficacy across all treated patients.

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- *Variable expression:* Administration of a single fixed dose to all patients prevents repeat dosing to adjust the expression level in each patient, called titration, and leads to variable levels of expression, with many patients expressing the therapeutic protein above or below target levels.
- *Inefficient clinical development:* Because patients cannot be redosed, those who do not achieve a therapeutic effect in early clinical trials cannot benefit from AAV therapy or contribute to further clinical development.
- *Inability to extend expression:* The antibodies formed following a single dose of AAV prevent re-treatment to increase or extend efficacy for patients with inadequate initial response or declining levels of expression.
- *Exclusion of pediatric patients:* The inability to redose precludes treatment of pediatric patients, whose organ growth and dividing cells would dilute expression over time.
- *Pre-existing immunity:* Up to half of patients have antibodies against AAV due to naturally acquired infections. These antibodies prevent them from receiving AAV gene therapy due to pre-existing AAV immunity to the capsid.
- *Payload capacity:* AAV constructs are limited to 4.7 kb in length, restricting both the size of genes and complexity of regulatory sequences that can be delivered. This restricts the diseases that can be addressed to those requiring single genes that can fit within this limited capacity and prevents the use of native regulatory sequences that may respond to the body's own signals.
- *Off-target, multi-tissue delivery:* Due to the inherent features of AAV, off-target delivery to unintended tissues and cell-types can lead to adverse events.
- *Quality control:* A lack of process and analytic control over the composition of AAV vectors leads to batch-to-batch variation in potency and potentially contributes to inconsistency in patients' responses.
- *Manufacturing scale:* The production systems for AAV gene therapies are limited in scale to 2,000 liters per batch or less. In general, the high doses required by AAV gene therapies and the low productivity of these systems combine to limit treatment to rare disease populations at a higher cost relative to other treatment modalities.
- *Payer coverage:* The relatively high cost of AAV gene therapies, combined with uncertain clinical durability and the inability to redose to extend expression, make it challenging for payers to predict clinical outcomes and, as a result, payers may be less inclined to pay for AAV gene therapies within the current reimbursement paradigm.

### *Gene editing*

Gene editing is the process of deleting, modifying or replacing defective DNA directly in the native genomic location. Zinc finger nuclease, TALEN and CRISPR-based gene editing are the most advanced approaches to gene editing and are currently in early clinical trials. CRISPR uses a combination of a nuclease to make a double-stranded break in the DNA and a guide RNA to direct the nuclease to the correct location for editing. Given insertion of full-length genes into the chromosome has remained relatively inefficient for gene editing, particularly *in vivo*, these approaches have primarily focused on *ex vivo* therapeutic applications.

Moreover, viral vectors are used widely to deliver gene editing nucleases *in vivo*, thereby conveying many of the same clinical and commercial challenges as viral gene therapy. Additional limitations for gene editing include the potential for unwanted DNA modifications related to double-stranded DNA breaks, the inability to control the level and duration of protein expression and low efficiency of precise gene correction.

### *Messenger RNA therapies*

Messenger RNA therapies are designed to increase mRNA levels by exogenous delivery of modified mRNA. However, the use of modified mRNA is limited by a lack of durable expression due to the half-life, or stability

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profile, of an mRNA transcript in the cell, which is approximately 10 hours. Due to the lack of durable expression for mRNA and the resulting requirement of frequent dosing, clinical development of mRNA therapies has focused primarily on novel vaccines. The safety of this frequent repeat dosing has yet to be proven clinically. In addition, the standard LNP approaches used for mRNA do not enable precise targeting of tissues.

### Summary of limitations of current approaches

The advancements in gene therapy have demonstrated the potential of these modalities to replace full genes and the aggregate market capitalization of publicly traded gene therapy companies in the United States exceeds \$50 billion. However, as illustrated in the figure below, the current approaches also have important limitations. While the development of our non-viral gene therapy platform is still in the early stage and we have not yet identified a product candidate, and thus contrasts with other approaches may not be a direct comparison, we have designed our platform to overcome the limitations of these gene therapy approaches.

### Comparison of genetic medicine approaches

FEATURE	AAV Gene Therapy	Gene Editing whole gene insertion	mRNA	generation bio	POTENTIAL BENEFITS TO STAKEHOLDERS
Durable	✓	✓	—	✓	<p>PATIENTS</p> <p>PHYSICIANS</p> <p>PAYERS</p>
Redosable	—	—	✓	✓	
Titratable	—	—	—	✓	
Large Genetic Payload	—	—	✓	✓	
Native Gene Regulation	—	✓	—	✓	
Tissue Specificity	—	—	—	✓	
Large Scale Manufacturing	—	—	✓	✓	

### Advantages of our non-viral gene therapy platform

Our non-viral gene therapy platform, comprised of our ceDNA construct, our ctLNP delivery system and our established, scalable capsid-free manufacturing process, is designed to overcome the limitations of current gene therapy approaches and we believe will disrupt the field of genetic medicine. We believe that our platform may provide the following advantages:

- **Durable expression:** Our ceDNA is highly stable and establishes extra-chromosomal episomes in the nucleus of cells to drive durable expression of the gene of interest. This durability has the potential to enable years-long expression for patients with each dose, minimizing the treatment burden for patients.
- **Redosable administration:** Our ctLNP system has been designed to avoid stimulating an antibody response in patients, thereby enabling redosing. The ability to redose provides several advantages:
  - **Individualized patient titration to reach desired expression level:** We expect our gene therapies will enable individualized patient titration, allowing each patient to be redosed until they reach the expression level required to address their specific needs. Patients and physicians may achieve individual therapeutic goals in a predictable manner.

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- *Greater opportunity to demonstrate efficacy in first-in-human trials:* Because we may be able to redose, we expect that a greater proportion of patients participating in our early clinical trials may achieve the desired level of gene expression.
- *Extending expression:* If expression of the gene of interest begins to wane for an individual patient, we expect that redosing could restore effective expression levels, prolonging the benefits of our therapies throughout the patient's life.
- *Reach pediatric patients:* Rapidly waning expression due to organ growth and dividing cells in children limits the utility of a single administration of gene therapy. We expect that the properties of our therapies may allow us to initiate treatment in childhood and allow the patient to prolong the benefits thereafter. Early intervention near the onset of disease may enable a greater therapeutic benefit throughout the patient's life.
- *Address untreated or under-treated patients:* Our therapies may be used to treat patients with pre-existing immunity to the AAV viral capsid, and therefore, not able to receive AAV gene therapy treatments, as well as patients whose efficacy outcomes on current gene therapy were insufficient in level or duration of expression.
- *Delivery of large genetic payloads:* The large payload capacity of ceDNA enables our constructs to carry large genes, multiple genes or combinations of genes with regulatory elements. This capacity arises from the lack of capsid packaging constraints that limit DNA incorporation in AAV gene therapy to less than 4.7 kb. Our established, scalable manufacturing process routinely prepares constructs of up to 12 kb without loss in yield or quality. We have not identified an upper limit of construct length.
  - *More potent constructs:* Our ceDNA constructs have the potential to improve upon existing gene therapy modalities by utilizing novel expression elements that exceed the capacity of AAV gene therapy.
  - *Larger genes:* Our ceDNA constructs may enable treatment of monogenic diseases requiring larger genes that are not possible to deliver with current gene therapy.
  - *Multiple genes:* Our ceDNA constructs have the potential to include novel multi-gene constructs to produce complex biologics such as monoclonal antibodies, or to address conditions that need more than one type of genetic correction.
  - *Native gene regulation:* The large capacity of our constructs provides us the ability to incorporate native regulatory elements that are naturally associated with the gene we are replacing. We believe this will allow for activity of the replaced gene to increase or decrease in response to the body's own signals.
- *Targeted, multi-tissue delivery:* Our ctLNP delivery system has been engineered to use biological ligands to reach receptors in a specific tissue. We believe that highly specific targeting to the key cell type for therapeutic benefit with limited delivery to off-target cells will improve the safety profile of our products.
- *Expected scale to reach millions of patients:* The combination of the expected multi-year durability of a single dose of ceDNA, tissue-specific delivery and manufacturing capacity may provide dosing for millions of patients living with prevalent diseases.
- *Sustainable payer model:* Our cost-effective manufacturing process combined with the potential to redose patients to extend expression may allow payers to better predict clinical outcomes and, as a result, to cover our therapies within the current reimbursement paradigm.

We believe that our new class of gene therapy has the potential to reach previously untreatable or under-treated patients and address new indications, including those with large patient populations, thereby unlocking the full potential of genetic medicine.

### **Our strategy**

Our goal is to become an industry leader in the field of genetic medicine, advancing our non-viral gene therapy platform to discover, develop, manufacture and globally commercialize a new class of gene therapy that is

durable, redosable and specifically delivered to a range of tissues for the treatment of diseases caused by single, large or multiple gene defects. We aim to provide sustainable, life-long treatment for millions of patients living with rare and prevalent diseases.

Key components of our strategy include:

- **Establish ceDNA as a new class of gene therapy, initially demonstrating its potential across rare monogenic diseases of the liver and retina.** We are prioritizing rare monogenic diseases of the liver and retina with significant unmet need for which our non-viral gene therapy platform may substantially improve clinical efficacy relative to current gene therapy approaches, beginning with hemophilia A, PKU, LCA10 and Stargardt disease. We believe our initial focus on these rare indications, which have well-established biomarkers and clear clinical and regulatory pathways, may enable us to achieve rapid human proof of concept, regulatory approval and eventually, commercialization. We expect to submit our first IND applications beginning in 2022.
- **Leverage our non-viral gene therapy platform to advance additional programs for diseases of the liver and retina and to expand quickly into additional tissues.** We are advancing additional programs for the liver and retina by making minimal changes to our ceDNA construct and by using the same ctLNP delivery system for each tissue. We believe this process can reduce the risk and accelerate the speed of development for subsequent indications in these tissues. We also plan to apply this approach as we develop biological ligands for our ctLNP delivery system to reach skeletal muscle, the CNS and tumors.
- **Utilize our eight-week research cycle to rapidly design, produce and screen ceDNA constructs to enable new disease programs within a tissue or therapeutic area.** We have established a highly efficient eight-week research cycle to rapidly design, produce and screen ceDNA constructs to enable new disease programs within a therapeutic area once human proof of concept is established in that area. We intend to invest in technologies to further accelerate our research cycle and create additional efficiency and scope for this process.
- **Expand manufacturing scale to access previously unattainable markets for gene therapy.** We have established a capsid-free manufacturing process for ceDNA that is scalable, cost-effective and yields a high-quality product using standard biological production equipment and engineering methods. We intend to further develop our internal manufacturing capabilities and to continue to expand our high-quality network of suppliers to increase capacity. We believe that our ability to conduct our manufacturing process at the 200-liter scale with high product quality suggests that further scaling to thousands of liters per batch is feasible using standard biological production equipment and engineering methods. We believe the combination of the expected multi-year durability of a single dose of ceDNA, tissue-specific delivery and manufacturing capacity may provide dosing for millions of patients living with prevalent diseases.
- **Expand patient access to our non-viral gene therapies through a high-value network of alliances and collaborations.** We are developing a broad and expandable portfolio of gene therapies that have the distinct opportunity to address rare monogenic diseases, as well as prevalent diseases. To help us realize the full breadth of opportunities and to expedite patient access to our gene therapies, we have established and plan to continue to explore a limited set of innovative collaborations and strategic alliances with biopharmaceutical companies whose capabilities and resources are additive or complementary to our own.
- **Build a sustainable leadership position in non-viral gene therapy as a fully integrated innovative biotechnology company.** We have established a leading position in non-viral gene therapy for gene transfer by investing in our ceDNA, ctLNP and manufacturing technologies and capabilities, and by rigorously protecting our innovations through an expanding intellectual property portfolio. We intend to evaluate and invest in new technologies that may further de-risk and accelerate the development of our new class of gene therapy, and to build out our capabilities to commercialize our gene therapies on our own.

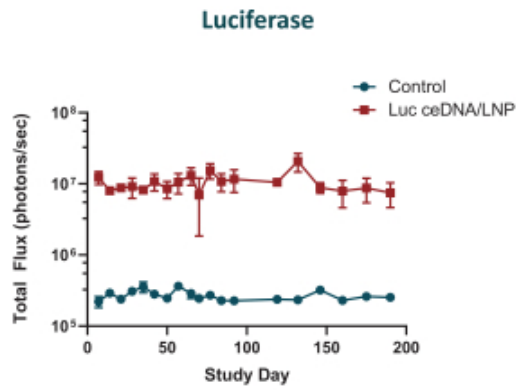
### **Our non-viral gene therapy platform**

Our non-viral gene therapy platform is comprised of three essential components: our high-capacity ceDNA construct, which can accommodate large or multiple genes as well as native regulatory elements; our ctLNP

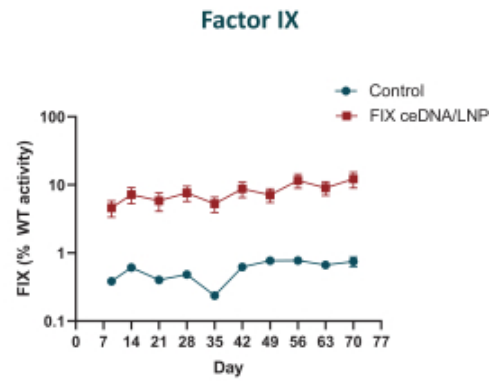
delivery system, which enables highly specific delivery of ceDNA to a range of tissues; and our established, scalable capsid-free manufacturing process, which uses a cost-effective biologics infrastructure that has the potential to reach patients with rare diseases and to expand access to patients with prevalent diseases, requiring millions of doses on a sustainable basis.

The three components of our platform are designed to enable critical features that address key limitations of existing genetic medicines. The ceDNA construct is designed to enable durable expression with a single dose. As shown in the figures below, in immunocompetent mice, a single intravenous dose of ceDNA formulated in an LNP provided months-long expression in the liver using both the reporter protein luciferase (denoted in the left figure below as Luc ceDNA/LNP) and human Factor IX, or FIX, the protein that is missing or defective in hemophilia B (denoted in the right figure below as FIX ceDNA/LNP).

**ceDNA-LNP: durable expression in immunocompetent mice after single IV administration**



- Single IV administration at study day 0
- Total flux measured by IVIS *in vivo* imaging

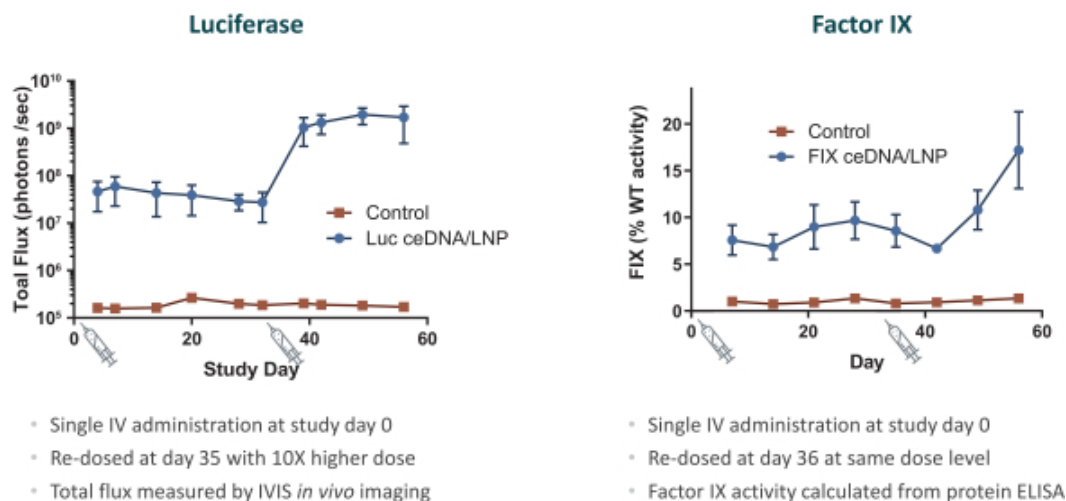


- Single IV administration at study day 0
- Factor IX activity calculated from protein ELISA



As shown in the figure below, ceDNA delivered in an LNP could be redosed in mice with normal immune systems because the first dose did not induce neutralizing antibodies. As the figure demonstrates, in immunocompetent mice, redosing ceDNA formulated in an LNP achieved increased expression using both reporter protein luciferase (denoted in the left figure below as Luc ceDNA/LNP) and human FIX (denoted in the right figure below as FIX ceDNA/LNP). In both studies, we intravenously administered ceDNA formulated in an LNP and then repeated the administration five weeks later. After the first administration of Luc ceDNA/LNP, mice demonstrated stable expression of luciferase protein and then higher, stable expression after repeat administration. After the first administration of FIX ceDNA/LNP, mice demonstrated 5-10% activity levels of FIX protein in the blood and then 10-20% activity after repeat administration. These results support our belief that our platform may enable us to titrate every patient to the desired level of protein expression.

**ceDNA-LNP: redosing achieves increased expression in immunocompetent mice**



As shown in the figure below, our upstream manufacturing process is comparable to biologics manufacturing and includes accumulation of ceDNA in Sf9 cells, which are then lysed to harvest ceDNA. The downstream process includes high-capacity purification of ceDNA drug substance, followed by ctLNP formulation. We have successfully completed ceDNA drug substance and purification runs of one liter, 50 liters and 200 liters, with a consistent processing time in the manufacturing plant of three weeks per run. With the process and controls we have developed, we achieve greater than 99% purity ceDNA following the downstream purification process, and have consistently demonstrated this up to the 200-liter scale.

## Overview of our capsid-free manufacturing process



### Closed-ended DNA (ceDNA) construct

ceDNA was discovered by our scientific co-founder Robert Kotin, who during his two decades as a senior investigator at the NIH also invented the Sf9 AAV production system and discovered the insertion site for AAV on chromosome 19. We have continued to build upon Dr. Kotin's work by assembling an expert team of leaders in molecular biology in order to deepen our understanding of ceDNA biology. In addition, we are expanding on Dr. Kotin's early work to create a broad palette of structural and sequence motifs for ceDNA constructs to explore novel mechanisms and to address multiple diseases. We are also deepening our expertise in computational biology, virology and cell biology to exploit the potential of large genomic datasets to elucidate the mechanisms underlying large subsets of prevalent and complex diseases.

ceDNA is an engineered, double-stranded, linear, covalently closed-ended DNA construct, with no free ends or viral capsid. As shown in the figure below, ceDNA includes the target gene or genes of interest, along with key components of the expression cassette, which is the full genetic sequence necessary to derive transcription including spacers, promoters and untranslated regions flanked by two inverted terminal repeat, or ITR, sequences. By gene of interest, we specifically mean the transcribed region of the target gene. ITRs, which are also present in AAV technology, are thought to be critical for durable expression in the nucleus of cells. To date, we have designed, produced and purified ceDNA constructs of up to 12 kb and have not identified an upper limit of construct length.

### ceDNA structure

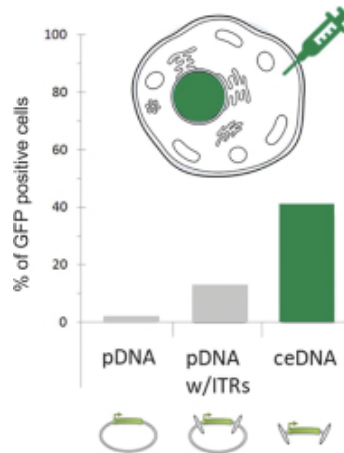


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### *Nuclear entry*

In an AAV system, it is thought that the capsid mediates nuclear entry. For our capsid-free non-viral gene therapy, we believe our ceDNA accesses the nucleus due to a previously unrecognized function of the ITR structure. In an *in vitro* study, we injected plasmid lacking ITR sequences, plasmid containing ITR sequences and ceDNA into the cytoplasm of individual cells. As shown in the figure below, the plasmid lacking ITR sequences was not able to access the nucleus, and the plasmid containing ITR sequences resulted in low but measurable expression. By contrast, ceDNA displayed positive green fluorescent protein, or GFP, expression, indicating that the ceDNA had effectively translocated to the nucleus.

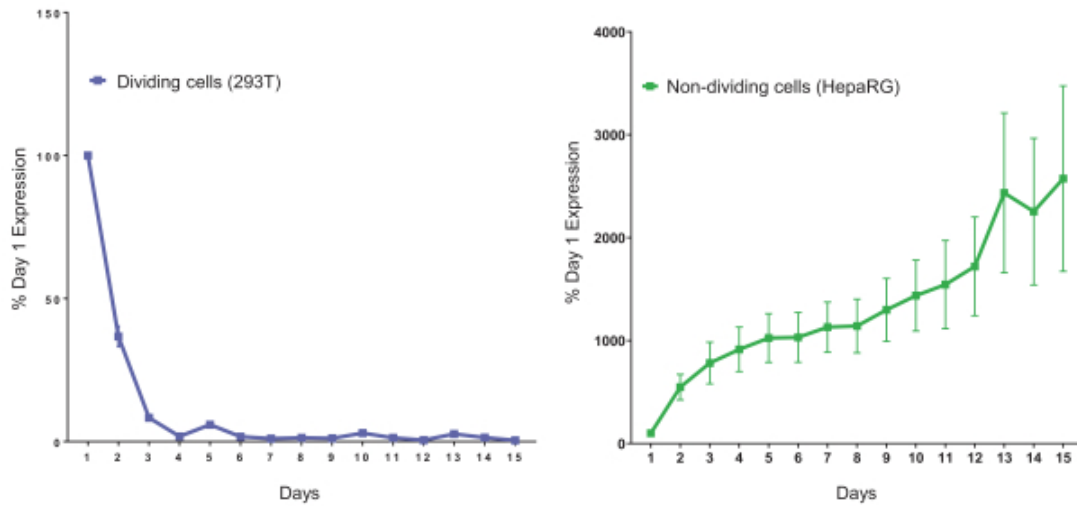
#### **ceDNA's ITR structure drives translocation to the nucleus**



### *Episomal expression*

ceDNA-derived expression has been observed in *in vivo* and *in vitro* studies to be episomal, meaning that it can deliver genetic material outside of the chromosome without being directly incorporated into or altering the cell's genome. This characteristic of ceDNA is a potentially important safety feature of our redosable gene therapy platform. In cell culture studies, as depicted in the figure below, the expression in dividing cells transfected with ceDNA encoding GFP decayed rapidly as the cells divided, consistent with lack of genomic integration as each successive cell division effectively diluted the amount of ceDNA in new generations of cells. In contrast, in cells transfected with ceDNA encoding GFP which are post-mitotic and therefore not dividing, we observed sustained and durable GFP expression over the course of two weeks.

**ceDNA-derived GFP expression observed to be episomal**



*ceDNA capacity*

The large payload capacity of ceDNA enables our constructs to carry large genes, multiple genes, or combinations of genes with regulatory elements. This capacity arises from the lack of capsid packaging constraints that limit DNA incorporation in AAV gene therapy to less than 4.7 kb. Our established, scalable manufacturing process routinely prepares constructs of up to 12 kb in length without loss in yield or quality. We have not identified an upper limit of construct length. We believe ceDNA can deliver a significant majority of the human coding sequences known to be relevant for the treatment of diseases that result from mutations in a single gene or in multiple genes. The practical applications of increased capacity include the ability:

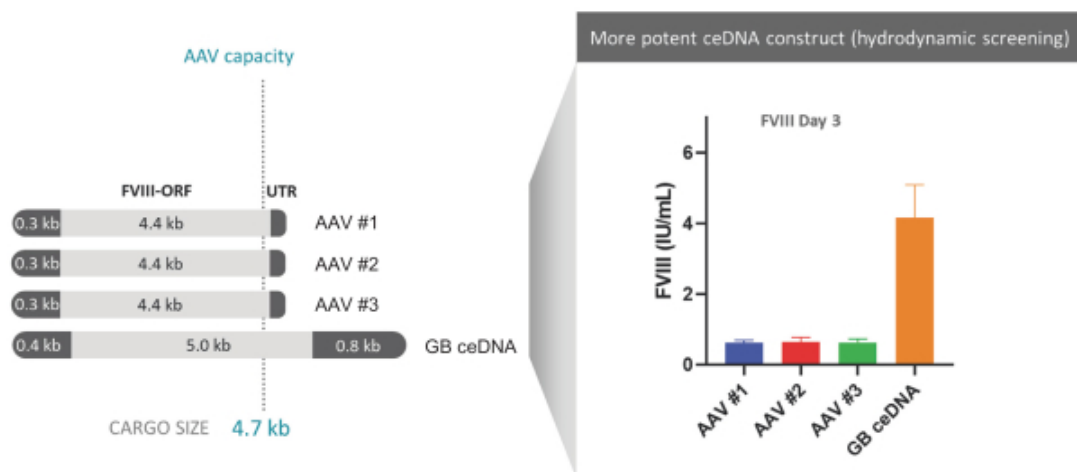
- to improve expression of existing targets of viral gene therapy and mRNA;
- to incorporate genes too large to be packaged in viral vectors;
- to include multiple genes, or to produce more than one transcript, which opens the possibility of creating several therapeutic molecules per ceDNA to address conditions that need more than one type of genetic correction; and
- to add native regulatory elements that are naturally associated with the gene we are replacing, which may allow for activity of the replaced gene to increase or decrease in response to the body's own signals.

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We have observed the impact of the increased payload capacity of our constructs on improved expression efficiency in *in vitro* and *in vivo* studies. We undertook studies of Factor VIII, a protein involved in the coagulation cascade. Defects in Factor VIII are known to give rise to hemophilia A. Factor VIII is a large protein having a minimal gene of interest domain accounting for 4.4 kb (in the B-domain deleted format) which is almost the entire AAV capsid capacity. For this reason, AAV Factor VIII constructs currently in clinical development contain the minimal, B-domain deleted coding region along with a small core promoter of 0.3 kb and limited transcriptional enhancer regions.

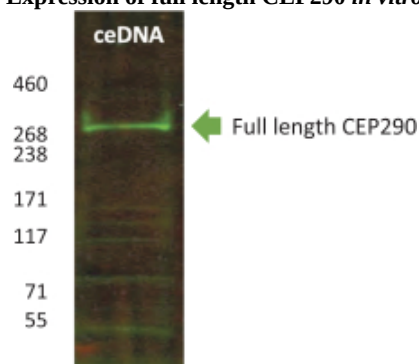
We have designed ceDNA constructs that have larger promoter elements and more substantial transcriptional enhancer regions than can be accommodated within the payload capacity of AAV. We have observed in a mouse model that a ceDNA construct, labeled as GB ceDNA in the figure below, showed six-fold improved expression of Factor VIII relative to ceDNA constructs with the expression cassette of each of three AAV Factor VIII product candidates currently in clinical development. The identification of constructs with improved potency may enable us to lower the dose required to achieve therapeutic efficacy.

### Increased ceDNA payload capacity enables the design of more potent constructs



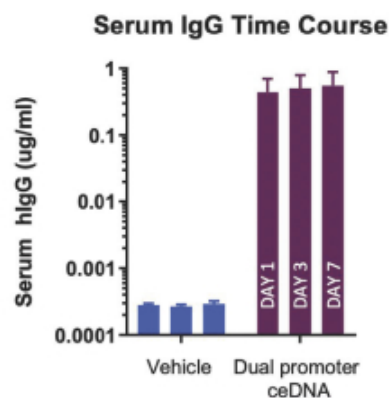
In addition to improving the activity of typical AAV target genes like Factor VIII, the capacity of ceDNA allows us to address monogenic diseases caused by large genes whose coding region is outside of the packaging capacity of AAV. One such example is LCA10, the most common genetic cause of childhood vision loss. LCA10 is caused by mutations in the CEP290 gene, which has a gene of interest region of 7.4 kb. Since this exceeds the payload capacity of AAV, there are no current transfer-based gene therapy programs in clinical trials for LCA10. By replacing the entire gene, gene therapy can potentially restore vision to patients with all forms of LCA10, irrespective of which mutation is present. We have created a ceDNA construct encoding the CEP290 gene that has demonstrated expression of full-length protein after transfection in cells, as shown in the immunoblot below.

**Expression of full length CEP290 *in vitro***



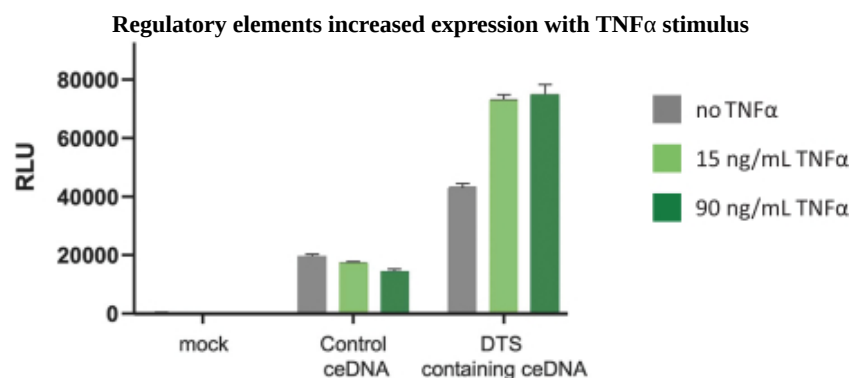
In *in vivo* studies, we have encoded and expressed two different proteins independently within the same ceDNA construct. To do this, we created a ceDNA that independently expressed heavy and light chain fragments of the antibody immunoglobulin, or IgG, with unique promoters for each, a requirement for producing distinct and separate proteins off one construct. Each promoter, a unique sequence that defines where DNA transcription starts, governs the independent production of its own transcript. This construct was able to produce fully formed and secreted IgG *in vivo*, as shown in the figure below. This ability to include novel multi-gene constructs to produce complex biologics, such as monoclonal antibodies, also opens the potential to address conditions that need more than one type of genetic correction, such as one that could knock down a gene and another that replaces a missing or defective gene.

**ceDNA dual promoter construct produced fully formed and secreted IgG *in vivo***



We have also shown in *in vitro* studies that our constructs can establish context-dependent expression by inclusion of regulatory sequences. The inclusion of regulatory sequences may enable expression of the therapeutic protein to adjust in response to changes in the patient's body, an example of which might be an anti-inflammatory antibody that is only expressed when the patient is in an inflammatory state. For these studies, we created a construct that contained multiple simian virus 40, or SV40, -derived nuclear factor kappa-light-chain-

enhancer of activated B cells, or NF $\kappa$ b, and DNA-targeting sequences, or DTS, that are known to be responsive to tumor necrosis factor alpha, or TNF $\alpha$ . As shown in the figure below, expression in HepG2 cells, as measured in reflected light units, or RLUs, was significantly increased in the presence of TNF $\alpha$  relative to control.



We believe this finding supports the potential to develop context-dependent expression cassettes and to take advantage of the sequence capacity necessary to accomplish this. Another example of such an application would be the inclusion of the native promoter in a construct expressing ABCB4 for progressive familial intrahepatic cholestasis type III where the native promoter is approximately 3.0 kb in size, which restricts its application in viral gene therapy. We have prepared this ceDNA and demonstrated that it expresses protein in cell culture.

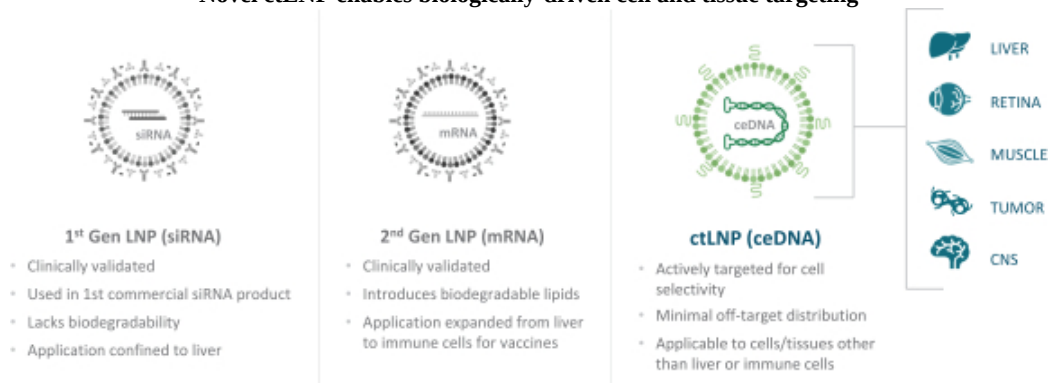
Our research and development of ceDNA has dramatically increased our understanding of the construct's properties, capabilities and *in vivo* functioning. We have filed numerous patent applications on our innovations in ceDNA structure, applications of the technology and specific classes of therapeutic ceDNA. We intend to continue investing in both ceDNA development and its intellectual property protection.

#### ***Cell-targeted LNP (ctLNP) delivery system***

Lipid nanoparticle technology has been developed over the past two decades for the effective delivery of nucleic acids to the liver, culminating in the first approved small interfering RNA, or siRNA, therapy for the treatment of transthyretin amyloidosis. Second-generation LNP technologies incorporate novel lipid components that improve potency, increase tolerability and are biodegradable. A second-generation LNP was recently clinically validated in a Phase 1 study of a passive immunization approach to Chikungunya virus. We have hired a team of chemists and formulation scientists along with cellular biologists and pharmacologists to advance our LNP technology and expertise.

Building on the attributes of both the first- and second-generation LNP technology, we have designed our ctLNP delivery platform so that its biodistribution can be selectively controlled through the addition of a targeting molecule, or ligand. In addition, our ctLNP may confer the advantages of predictable behavior across species, minimal off-target effects, and a foundational platform approach that unlocks the ability to delivery to other tissues, including retina, skeletal muscle, the CNS and tumors. The graphic below illustrates the evolution from first generation LNPs to ctLNP.

**Novel ctLNP enables biologically-driven cell and tissue targeting**



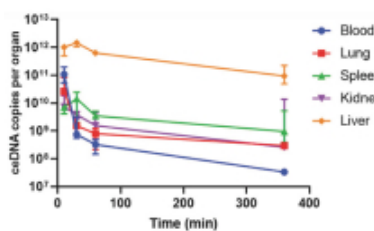
A key feature of our ctLNP technology is the use of biological targeting ligands. This is a strategy that is shared with antibody-drug conjugates and with oligonucleotide conjugates, both of which have demonstrated clinical success. The application of targeting ligand technology has historically been unavailable to nanoparticles. This is primarily due to the non-specific and efficient uptake of nanoparticles by cells of the reticuloendothelial system, or RES, a system of cells that removes immune complexes and foreign particulates from circulation in healthy persons, and historically overwhelms the effectiveness of the targeting ligand. We have applied our chemistry and formulation capabilities to identify LNPs that avoid RES-mediated clearance, which has enabled the use of biological targeting ligands. We have achieved proof of concept for tissue-specific delivery with ctLNP *in vivo* for liver and retina and *in vitro* for skeletal muscle.

*Liver*

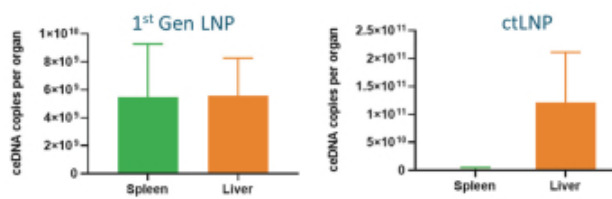
We have employed N-acetyl galactosamine, or GalNAc, as the ligand of choice for targeting the majority of liver cells, called hepatocytes, specifically in the liver through the asialoglycoprotein receptor, or ASGPr, a well validated, selective ligand-receptor pair for delivery to hepatocytes that is conserved across species including mouse, rat, non-human primates and humans. Prior third-party research has shown that the pharmacology of the ASGPr receptor in non-human primates is strongly correlated with the pharmacology of the ASGPr receptor in humans. GalNAc targeted oligonucleotides have also demonstrated broad distribution to all hepatocytes. When we dosed GalNAc targeted ctLNPs in mice, we observed a profound selectivity for ceDNA delivery to the liver. As shown in the left figure below, ceDNA was distributed selectively to the liver, with more than 97% of the total ceDNA copies in that tissue. By contrast, less than 3% of the copies per tissue was present in blood, lung, spleen and kidney combined. This stands in contrast to first generation LNPs, as shown in the middle and right figures below. At six hours post administration, first generation LNPs distribute equal ceDNA copies in spleen relative to liver. In contrast, distribution of ceDNA with ctLNP is highly selective for liver at this time point. This selectivity enhancement of ctLNP relative to first-generation LNP minimized off-target effects and enabled well-tolerated dosing up to 5.0 mg/kg in mice. When we examined the liver tissue by *in situ* hybridization, we observed up to 100% of hepatocytes transduced with ceDNA at early time points, highlighting the breadth of distribution of ctLNP. Additionally, we have demonstrated the successful dosing of a ctLNP in preliminary non-human primate experiments at doses up to 0.5 mg/kg. The 0.5 mg/kg ctLNP dose level was tolerated and not associated with signs of hepatotoxicity.



**ctLNP Longitudinal PK in mice**

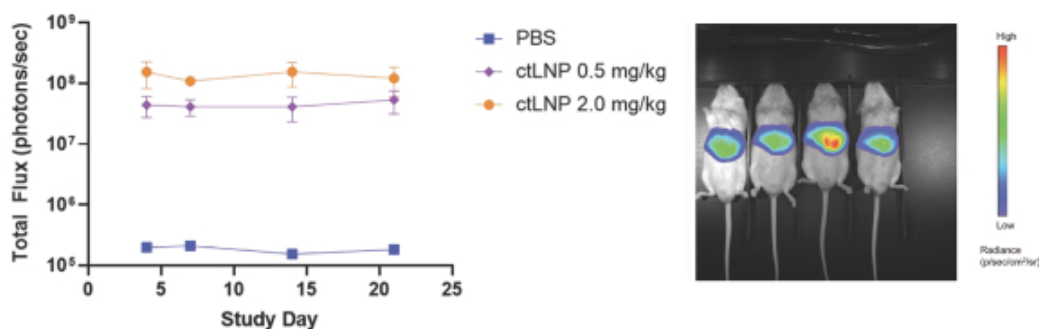


**Biodistribution by tissue at 6hr for 1<sup>st</sup> Gen LNP**



We have demonstrated in mice both high-level and dose-dependent expression from ceDNA incorporating our ctLNP system using a reporter ceDNA that expresses firefly luciferase after a single intravenous administration on day one. The expression was also determined to be dose proportional as we increased the ctLNP from 0.5 mg/kg to 2.0 mg/kg, as shown in the left figure below. The protein expression was specific to the liver region as determined by in-life imaging, as shown in the right figure below. We continue to apply chemistry and formulation optimization efforts to improve the activity of ctLNP, with our latest ctLNPs providing three to five times improvements in expression over our first iteration. We plan to continue to make further improvements in this technology.

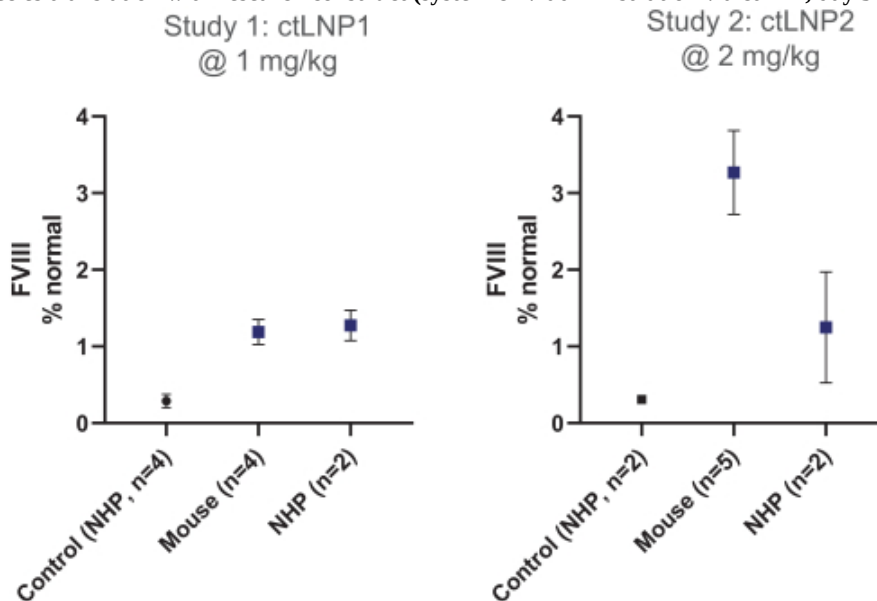
**High-level and dose-dependent luciferase expression from ceDNA-ctLNP**



In two further *in vivo* studies, we demonstrated translation of expression from mice to non-human primates and confirmed delivery of ceDNA to the liver via ctLNPs in non-human primates. In the studies, we delivered the same weight-adjusted dose of a ceDNA construct in each species systemically via a liver-directed ctLNP and observed an approximately 2:1 species translation from mice to non-human primates. In the first study, we observed a mean human factor VIII expression level of approximately 1% of normal levels in mice at day 7 following a single 1.0 mg/kg dose of the ceDNA construct and a mean human factor VIII expression level of approximately 1% of normal levels in non-human primates at day 5 using identical material and weight-adjusted dosing (1.0 mg/kg) as shown in the left figure below. In the second study, employing a slightly different ctLNP, we observed a mean human factor VIII expression level of approximately 3% of normal levels in mice at day 5 following a single 2.0 mg/kg dose of the ceDNA construct and a mean human factor VIII expression level of approximately 1% of normal levels in non-human primates at day 5 using identical material and weight-adjusted dosing (2.0 mg/kg) as shown in the right figure below.

All doses in mice and non-human primates were well-tolerated up to the highest dose of 2.0 mg/kg. There were no adverse clinical observations, changes in clinical pathology, or histopathology findings including in the liver and spleen in non-human primates.

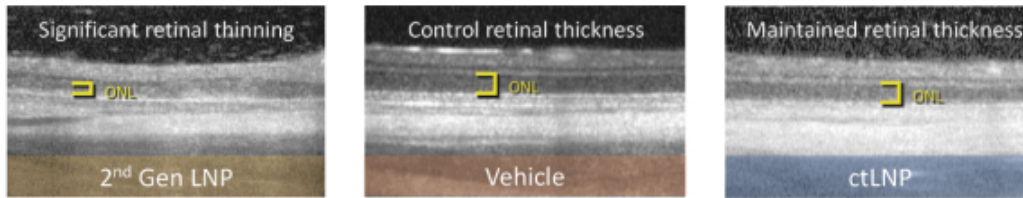
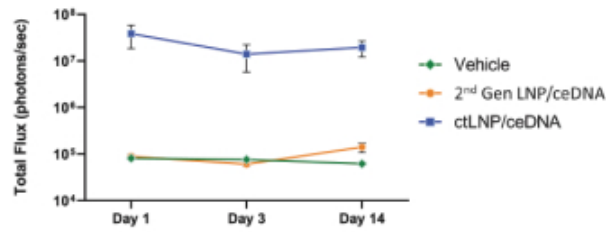
Species translation with research construct (systemic IV administration via ctLNP, day 5 or 7)



Retina

In addition to assessing the specificity and activity of ctLNP established for systemic administration to the liver, we have also assessed ctLNP in local administration to the retina in the eye. Second-generation LNPs containing ceDNA, when dosed subretinally *in vivo* in rats, led to significant inflammation and retinal degeneration and failed to express protein. This degeneration is evident by measuring the thickness of the outer nuclear layer, or ONL, by optical coherence tomography imaging, shown in the yellow labels in the figures below. By contrast, administration of ctLNP subretinally *in vivo* in rats led to high levels of expression and lack of retinal degeneration at day 21. We believe this improved retinal tolerability profile is due to ctLNP avoiding off-target delivery to local immune cells. We have additionally demonstrated efficient transduction of retinal photoreceptor and retinal pigment epithelial, or RPE, cells with ctLNP, which we believe enables disease relevant expression for our lead retinal programs, LCA10 and Stargardt disease.

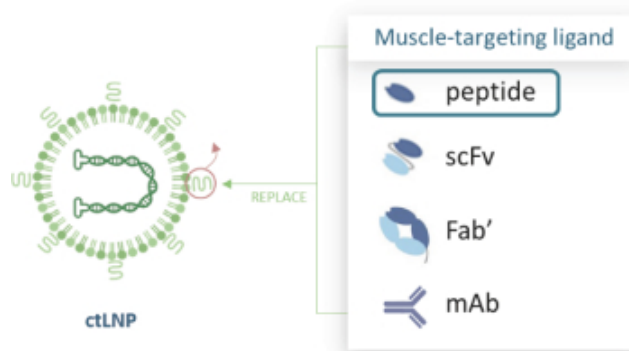
### Subretinal injection of ceDNA-ctLNP led to high levels of expression and lack of retinal degeneration



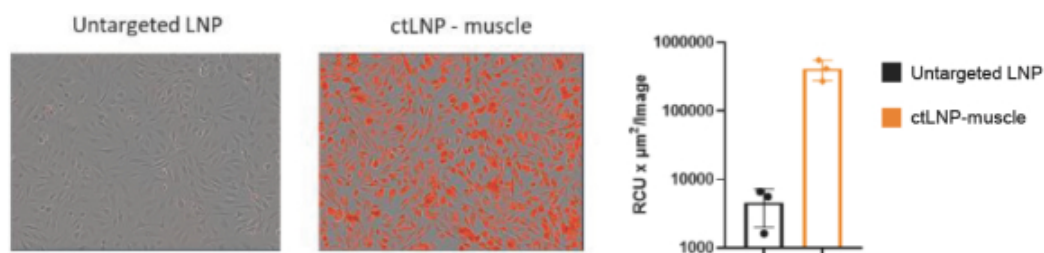
### Skeletal muscle

We have identified a number of potential ligands for skeletal muscle and have been able to conjugate peptide-based ligands to ctLNP that have enhanced uptake into a differentiated skeletal muscle cell line, or myocyte, *in vitro*. These peptide-based ligands target known receptors, such as the transferrin receptor that is present on the surface of skeletal muscle. ctLNPs that include these peptide-based ligands on the surface of the particle show high levels of uptake in muscle cells in culture. We have observed this in *in vitro* studies in which we included a red dye in the ctLNP enabling quantification of uptake into these cells, as shown in the figure below. We are pursuing muscle-targeted ctLNPs for *in vivo*, systemic administration to target skeletal muscle and replace missing or defective genes, such as dystrophin in Duchenne Muscular Dystrophy.

### ctLNP targeting skeletal muscle using peptide ligand



### Enhanced uptake in c2c12 myocytes



LNPs are one of the most advanced non-viral delivery solutions for nucleic acid therapeutics. We have built on the attributes of the second generation of clinical LNPs, which include improved tolerability through utilization of biodegradable lipids. Specifically, we have engineered our ctLNP to allow for active targeting of specific cell types *in vivo*. Targeted delivery of DNA *in vivo* without incurring innate immune reactions has long been a challenge in the field. The profile of our ctLNP has led to further improvements in tolerability, increased delivery efficiency and application to tissues beyond liver and immune cells. Our ctLNP delivery system has shown proof of concept *in vivo* in liver and retina with *in vitro* proof of concept for skeletal muscle. We plan to continue to seek to optimize ctLNP for use in liver, retina and skeletal muscle and to expand its application across a range of tissues, including the CNS and tumors. We have filed numerous patent applications to solidify our leadership in this area, including ones covering fundamental LNP technology as well as methods to avoid or reduce immune response.

### Established, scalable manufacturing

Since our founding, we have invested in internalizing core development capabilities to build our manufacturing processes and analytical testing as a point of strength. We have recruited a seasoned team of development and manufacturing experts who have enabled more than 20 INDs and negotiated multiple product launches, including for both a cell and a gene therapy product.

Additionally, we have built state-of-the-art development laboratories to create novel upstream and downstream processes as well as analytical methodologies that have shifted the product profile from early research efforts of approximately 10% pure ceDNA to one that is consistently greater than 99% pure ceDNA. Our current internal development efforts are focused on industrialization of the process to enable unit operations that are scalable using standard biological production equipment.

Our established, scalable manufacturing employs a proprietary, capsid-free process and utilizes standard biologics infrastructure, unlike traditional viral gene therapy manufacturing. Viral gene therapy relies on a protein capsid for therapeutic delivery of a viral vector, and as a result, the manufacturing process for viral gene therapies requires the production of protein capsids, which limit process scalability and consistency. Our capsid-free manufacturing process is an efficient and reproducible process that includes rigorous, industrial-scale purification that consistently yields greater than 99% pure ceDNA.

We have completed ceDNA drug substance and purification runs of one liter, 50 liters and 200 liters, with a consistent processing time in the manufacturing plant of three weeks per run, and greater than 99% purity ceDNA following the downstream purification process.

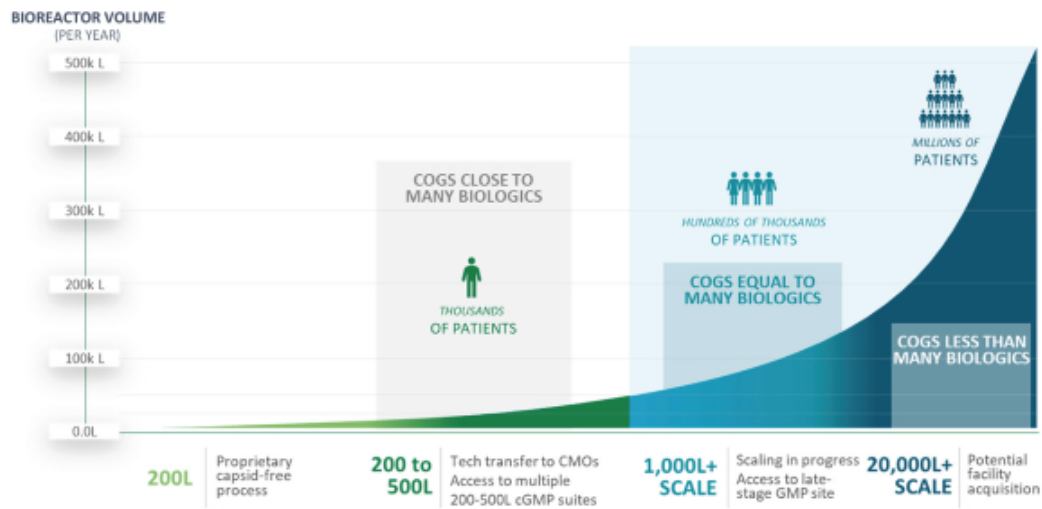
We now routinely produce material at 50-liter scale internally to support research studies, and our CDMOs have produced material at 200-liter scale, using our cGMP-ready process, to supply IND-enabling preclinical studies and early clinical trials. Additional development efforts have been initiated to further scale the process to thousands of liters.

The scalability and productivity of the manufacturing process is a significant driver of the cost-effectiveness of any therapeutic. We believe being able to produce ceDNA at a scale of thousands of liters per batch should

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enable a significant reduction in our overall cost of goods, and our goal over time is to be competitive with traditional biologics in scale and cost. We believe that our ability to conduct our manufacturing process at the 200-liter scale with high product quality suggests that further scaling to thousands of liters is feasible using standard biological production equipment and engineering methods.

### Significant cost and scale advantage, eventually comparable to biologics



Our ongoing work in manufacturing technology has led to numerous innovations in production processes and analytics, some of which may have broader applications in related fields. We continue to seek to protect the full reach of these discoveries through both patent application filings and as trade secrets.

### Summary

We believe our non-viral gene therapy platform represents a powerful product engine fueled by ceDNA, which in preclinical studies has provided durable episomal expression with large capacity, and our highly selective and modular ctLNP delivery system. We have designed the combination of these platform components with a goal of enabling a broad and expandable product portfolio that can be deployed against a range of tissues, including liver, retina, skeletal muscle, the CNS and tumors. These characteristics are supported by our established, scalable capsid-free manufacturing process, which supports the potential to extend the reach of gene therapy beyond rare diseases to prevalent diseases.

### Our integrated research and development approach

Our development strategy is differentiated and informed by our extensive experience in rare disease drug development, regulatory engagement and commercialization. We are focused on diseases with significant unmet need for which our non-viral gene therapy platform may substantially improve clinical efficacy relative to current gene therapy approaches. We are initially prioritizing rare monogenic diseases of the liver and retina that have well-established biomarkers and clear clinical and regulatory pathways. We plan to incorporate redosing in our first-in-human clinical trials, which may allow us to reach the desired therapeutic expression level in every patient, providing early and robust human proof concept.

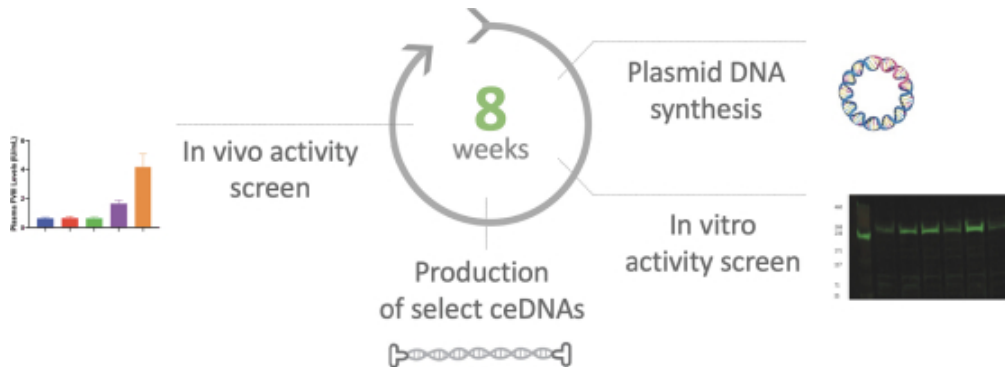
In parallel, we are developing the constructs and manufacturing capacity for programs to address additional rare and prevalent diseases. We have established a highly efficient eight-week research cycle to rapidly design, produce and screen ceDNA constructs to enable new disease programs within a tissue once human proof of

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concept is established. By leveraging a common ctLNP for each tissue, we believe we can reduce the risk and accelerate the speed of development for subsequent indications.

Our research cycle, illustrated in the figure below, utilizes *in vitro* activity screens of novel plasmid DNA designs, followed by *in vivo* activity screens of select ceDNA constructs. We have iteratively employed this cycle to rapidly identify ceDNA constructs that achieve disease correction in animal models and have observed that learnings from our more mature programs accelerate our ability to identify effective ceDNA constructs for subsequent indications.

### Our eight-week research cycle rapidly identifies ceDNA constructs for new programs



We plan to apply this integrated research and development strategy across liver, retina, skeletal muscle, oncology and the CNS.

### Our portfolio

We are advancing a broad and expansive portfolio including programs for rare and prevalent diseases of the liver and retina. We are focused on diseases with significant unmet need for which our non-viral gene therapy platform may substantially improve clinical efficacy relative to current gene therapy approaches. We are initially prioritizing rare monogenic diseases of the liver and retina that have well-established biomarkers and clear clinical and regulatory pathways. We plan to expand our portfolio to include rare and prevalent diseases of the skeletal muscle, the CNS and oncology by developing discrete ctLNPs, each engineered to reach a different tissue. As shown in the figure below, our most advanced liver disease programs are in hemophilia A and PKU, which are in the preclinical stage of development, and our most advanced retina disease programs are in LCA10 and Stargardt disease, which are in the lead optimization stage of development.

In addition, we believe that our non-viral gene therapy platform may allow patients to produce antibody therapies from their own cells for years at a time from a single dose and plan to advance programs to deliver antibody genes, directing the body's own cells to express and secrete therapeutic antibodies. We believe the combination of the expected multi-year durability of a single dose of ceDNA, tissue-specific delivery and manufacturing capacity may provide dosing for millions of patients living with prevalent diseases.

THERAPEUTIC AREA	PROGRAM	US PREVALENCE*	PORTFOLIO					* PREVALENCE DATA ARE APPROXIMATE	
			RESEARCH	LEAD OPTIMIZATION	PRE-CLINICAL DEVELOPMENT	PHASE 1 CLINICAL	PHASE 2 CLINICAL	PIVOTAL CLINICAL	
Liver	Hemophilia A	16,000	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
	PKU	15,000	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
	Wilson Disease	11,000	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
	Gaucher Disease	6,000	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
	Antibody gene therapy		[Progress bar: Research]						
Retina	LCA10	2,200	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
	Stargardt	37,000	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
	Wet AMD	1,200,000	[Progress bar: Research, Lead Optimization, Pre-clinical Development]						
EXPANSION OPPORTUNITIES : Skeletal Muscle   Oncology   CNS									
<b>NEXT STEPS</b> <ul style="list-style-type: none"> <li>1 Two development candidates to be selected in 2021</li> <li>2 IND-enabling studies in two indications in 2021</li> <li>3 First INDs submissions beginning in 2022</li> <li>4 Additional INDs anticipated in 2023 and beyond</li> </ul>									

Within the therapeutic area of the liver, we have established programs for inborn errors of metabolism in PKU and Wilson disease. We are also advancing programs for systemic disorders in which the liver can be utilized to secrete therapeutic proteins in hemophilia A, Gaucher disease and antibody gene therapy.

We plan to utilize our eight-week research cycle to rapidly design, produce and screen ceDNA constructs for other diseases within a tissue, so that we may rapidly expand clinical development efforts to include additional rare and prevalent diseases once human proof of concept is established in that tissue. For instance, if human proof of concept is established in PKU, we plan to rapidly expand our development efforts to include additional inborn errors of metabolism such as progressive familial intrahepatic cholestasis 2, or PFIC2, glycogen storage disease type 1a, or GSD1a, and ornithine transcarbamylase deficiency, or OTC. Similarly, if human proof of concept in hemophilia A is established, we plan to expand our programs in other diseases requiring secretion of therapeutic proteins such as Gaucher disease, Pompe disease, hereditary angioedema, or HAE, alpha1-antitrypsin deficiency, or A1AT, antibodies against Cov-2 and human immunodeficiency virus, or HIV.

We plan to apply this strategic approach of rapid expansion following initial human proof of concept in a therapeutic area across our portfolio.

### Liver diseases

For the majority of our liver programs, we have designed and manufactured disease-modifying ceDNAs that have shown expression *in vitro* and/or disease correction *in vivo*. We have employed GalNAc as the targeting ligand in our ctLNP delivery system to selectively drive biodistribution to the liver. GalNAc binds to the ASGPr on hepatocytes, and the biology of this selective ligand-receptor pair for delivery to hepatocytes has been well validated in human clinical trials. For each liver program, we plan to formulate ceDNA within a ctLNP-GalNAc expressing the relevant gene of interest for intravenous delivery. GalNAc targeting has been demonstrated to efficiently deliver ceDNA to up to 100% of hepatocytes and we believe that broad biodistribution of ctLNP-GalNAc to hepatocytes will be a key strength of our pipeline programs since current gene therapy approaches deliver payload to 30% or fewer of hepatocytes with a single dose. Additionally, our potential to redose patients until they are in the therapeutic range of expression may enable early and robust human proof of concept in Phase 1/2 clinical trials and is a key differentiator from current gene therapy approaches.

### Hemophilia A

#### Overview

Hemophilia A is a rare X-linked hereditary bleeding disorder characterized by impaired blood coagulation as a result of deficiencies in the production or function of coagulation Factor VIII. There are approximately 16,000 hemophilia A patients in the United States and 320,000 patients worldwide. Because of the deficiency of

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coagulation Factor VIII, hemophilia A patients bleed in joints, muscles, soft tissues and within mucous membranes, which can be either spontaneous or due to internal or external trauma, depending on the severity of the disease. The clinical presentation of hemophilia A can be mild, moderate or severe, depending on the residual level of circulating Factor VIII. The diagnosis of hemophilia A is often made at a young age, earlier than 36 months, based on persistent bleeding or internal hemorrhage.

### *Current approaches and limitations*

Most patients with hemophilia A in the United States and the European Union are currently treated with clotting factors according to practice guidelines, which are relatively consistent around the world. Children are generally treated prophylactically, while adults may be treated either prophylactically or on demand, depending on the residual level of Factor VIII activity in the blood. Compliance with clotting factors is 50% to 80%, and up to 30% of patients with severe disease develop inhibitors to Factor VIII replacement. Approximately 75% of hemophilia A patients worldwide still receive inadequate treatment or have no access to treatment.

HEMLIBRA (emicizumab) is a bispecific Factor IXa- and Factor X-directed antibody indicated for routine adult and pediatric patients ages newborn and older with hemophilia A. However, this product has safety concerns as several cases of thrombotic microangiopathy/thrombosis have occurred, in some cases in the context of co-administration of activated prothrombin complex concentrate.

There are several AAV gene therapies currently in late-stage clinical trials, including Valrox (valoctocogene roxaparvovec), for which a biologics license application, or BLA, is under review by the FDA. Early data from these trials have shown variation in the amount of Factor VIII expressed from patient-to-patient with a substantial proportion of patients either becoming suprathreshold or remaining subtherapeutic after Valrox administration. Many hemophilia A patients have pre-existing immunity to AAV and, therefore, are not candidates for this therapy. Mean Factor VIII levels decline over two to three years after treatment with Valrox, which means that it is possible that patients will become subtherapeutic over three to five years and cannot be redosed with AAV gene therapy. In addition, AAV gene therapy will not be available to children with hemophilia A since their livers are still growing and only one dose is possible.

There are no current or investigational therapies that have been shown to durably induce therapeutic Factor VIII levels in all patients of all ages, nor therapies that can be redosed when Factor VIII expression wanes through the life of the patient. Given the variable response to gene therapy in patients with hemophilia A, titration at onset of therapy is critical to ensure that all patients get within a therapeutic range. Since there are potential consequences to expressing too much Factor VIII, such as excess blood clotting, the ability to titrate the therapy will enable an optimal dosing regimen.

### *Our approach*

Our gene therapy approach aims to do the following in hemophilia A:

- achieve therapeutic Factor VIII levels in patients of all ages, resulting in normalization of bleeding risk;
- treat infants and children to prevent bleeds early in disease and prevent irreversible tissue and organ dysfunction;
- achieve the desired level of gene expression in a greater proportion of patients participating in our early clinical trials through our ability to redose;
- ensure that all patients achieve curative levels of Factor VIII of greater than 25% of normal activity levels with the ability to titrate expression to higher target levels for some patients as needed based on lifestyle and circumstances;
- deliver ceDNA-FVIII to a large percentage of hepatocytes resulting in a relatively low burden of expression for each hepatocyte, which may lead to more durable expression compared to other gene therapy modalities; and

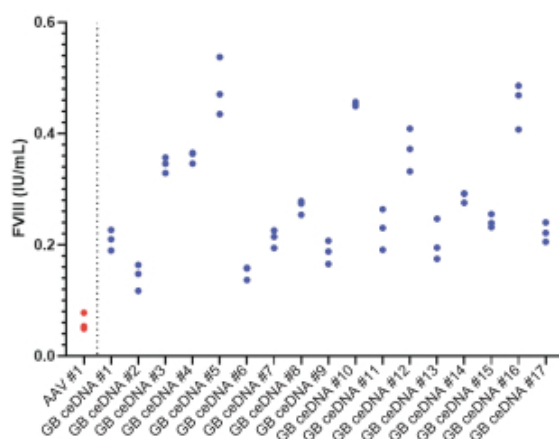


- increase the safety index by achieving therapeutic Factor VIII levels at lower doses because of more potent ceDNA-FVIII constructs and greater hepatic biodistribution.

Our approach has the potential to titrate expression in each patient to reach target Factor VIII levels, avoiding supratherapeutic levels and minimizing the thrombotic, or clotting, risk to the patient. In addition, we can potentially treat patients for life by episodically following Factor VIII levels and redosing as needed, should expression wane over time. Redosing may also enable broader access for all patients with severe disease, and for children with mild to moderate disease severity who are currently managed through on-demand treatment, as shown in the right figure below.

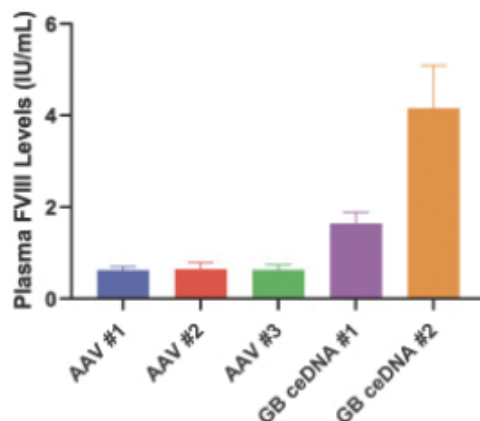
We have created multiple distinct ceDNA-FVIII constructs with different expression cassette elements, including promoter, intron, untranslated regions, or UTRs, and codon optimization sequences. *In vitro* screening of ceDNA-FVIII constructs revealed that several constructs express Factor VIII, as defined by functional activity measures, as shown in the figure below. All of our ceDNA constructs, labeled as GB ceDNA in the figure below, expressed greater activity of FVIII compared to a ceDNA construct with the expression cassette of an AAV-FVIII product candidate that is currently in clinical trials, AAV #1, with some expressing up to six-fold more Factor VIII activity.

### Several ceDNA-FVIII demonstrated greater activity compared to AAV-FVIII



The enhanced potency of our ceDNA-FVIII constructs has also been confirmed *in vivo*. In an *in vivo* study, we measured serum levels of human Factor VIII after hydrodynamic injection of various ceDNA constructs into the tail vein of mice and assessed protein levels by enzyme-linked immunosorbent assay for human Factor VIII. As shown in the figure below, two ceDNA constructs listed as GB ceDNA #1 and GB ceDNA #2 demonstrated 1.0 and 6.0 IU/ml Factor VIII activity, or 100% and 600% of normal levels, respectively. In contrast, at the same dose, ceDNA constructs with the expression cassette of each of three AAV-FVIII product candidates currently in clinical development, demonstrated approximately 0.5 IU/ml Factor VIII activity, or 50% of normal levels in animals.

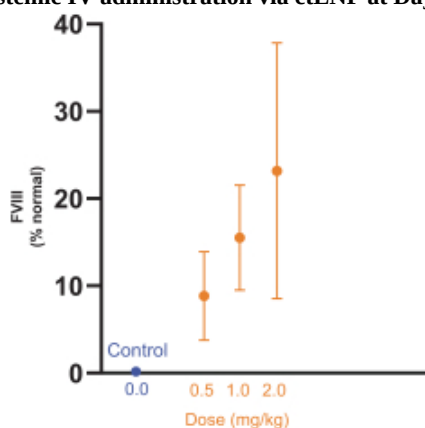
**In vivo activity of ceDNA-FVIII constructs**



The direct relevance of having more potent ceDNA constructs is that the input dose required to have a therapeutic effect may be lower, thereby increasing the safety profile and lowering the metabolic requirements on individual hepatocytes to produce and secrete Factor VIII.

In a separate *in vivo* study, we achieved targeted levels of human factor VIII expression in hemophilia A mice at day 10 following a single dose of a ceDNA construct delivered systemically via a liver-directed ctLNP. In this study, which was conducted in three cohorts, we observed a dose-response relationship with a mean human factor VIII expression level of 23% of normal levels following a dose of 2.0 mg/kg, a mean human factor VIII expression level of 16% of normal levels following a dose of 1.0 mg/kg and a mean human factor VIII expression level of 9% of normal levels following a dose of 0.5 mg/kg as shown in the figure below. The doses were well-tolerated by the hemophilia A mice at all dose levels.

**Expression of FVIII in mice dosed with hemophilia A development construct (systemic IV administration via ctLNP at Day 10)**



The approximately 2:1 expression ratio from mice to non-human primates that we historically observed is similar to expression ratios from mice to non-human primates observed across other modalities delivered via LNPs, including RNA interference and mRNA, and we believe establishes a basis for us to select a development candidate in our hemophilia A program. The expression levels in mice using a ceDNA construct, coupled with

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the approximately 2:1 expression ratio from mice to non-human primates and the expected 1:1 translation from non-human primates to humans that has been established for LNPs, support the selection of a final hemophilia A clinical development candidate. The expression levels we observed may correspond to or exceed the human factor VIII expression level of 5% of normal levels that has been clinically demonstrated to prevent serious bleeds in patients.

### Next steps

We anticipate achieving proof of concept for biodistribution and durable expression in non-human primates using our ctLNP with a reporter protein such as Factor IX in 2021. We plan to begin IND-enabling studies in 2021, and to submit an IND application for this program in 2022.

## Phenylketonuria

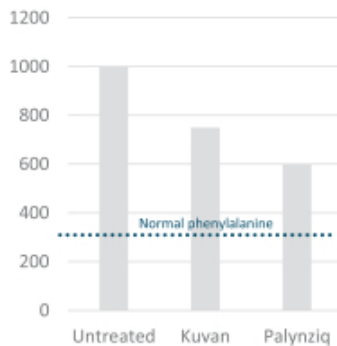
### Overview

PKU is a rare autosomal recessive genetic disorder caused by deficiency of the hepatic enzyme phenylalanine hydroxylase, or PAH, that metabolizes the essential amino acid phenylalanine, or Phe, to tyrosine, or Tyr, an essential amino acid for CNS development and function. PAH deficiency leads to elevated levels of Phe in the blood and toxic Phe accumulation in the brain resulting in neurocognitive manifestations including failure to attain early developmental milestones and progressive impairment of cerebral function. Patients with uncontrolled severe PKU will develop profound neuropsychiatric disorders and irreversible intellectual disability.

There are approximately 15,000 patients with PKU in the United States and 41,000 patients in the European Union. PKU is usually diagnosed at birth through newborn screening, which provides the opportunity to introduce therapies that reduce Phe levels. However, as shown in the left figure below, without strict dietary control, current therapies do not normalize Phe levels. Attaining consistent levels of Phe in childhood is correlated with higher IQ levels and executive functioning in adults, and short-term spikes in Phe result in long-term impairment of neurocognitive function, as shown in the middle figure below. Even without optimal correction of Phe levels in childhood, control in adolescent and adult PKU patients has been shown to result in higher levels of executive function and attention and lower levels of depression and anxiety. As shown in the right figure below, adolescents are unable to maintain such a strict diet, with 50% of patients age 10-14 above the recommended Phe levels and almost 80% of patients outside the normal Phe range in the late teen years.

### Early consistent Phe normalization key to neurocognitive outcome

Without strict diet, current therapies do not normalize phenylalanine

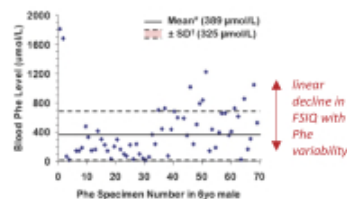


Based on data from Blau et al., Mol. Genet. Metab. 96: 158-163 (2009)  
Longo et al. Lancet 384(9937): 37-44 (2014)



Children with PKU on diet have lower IQ than unaffected peers or sibling controls

Short-term spikes in blood Phe result in long-term impairment of mental function

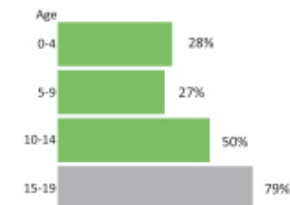


Based on data from Anastasakis et al., Molec. Genet. Metab. 95: 17-20 (2008)  
Waisbren, Children's Hospital Boston



High dietary non-compliance in PKU patients increases during crucial developmental period

% of patients above recommended Phe levels



Based on data from Waisbren, Children's Hospital Boston, adapted from Walter et al., Lancet 360: 55-57 (2002)

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### *Current approaches and limitations*

The standard of care for PKU is strict, life-long dietary modification to control blood Phe levels to the recommended target range of 120 to 360 micromoles per liter. This requires PKU patients and caregivers to carefully monitor diet and severely restrict protein intake and other Phe-rich foods. Medical foods including formula and foods modified to be low in protein are also required.

Initiation of a Phe-restricted diet is recommended as early as possible in infancy to avoid irreversible neurocognitive decline due to elevated Phe levels. While this allows some patients to approach target Phe levels, it is challenging to maintain as a life-long treatment. Even with full compliance of dietary therapy during childhood, many patients have episodic or chronic high Phe levels and suffer irreversible neurocognitive impairment as a result.

PALYNZIQ (pegvaliase) and KUVAN (sapropterin dihydrochloride), a biologic and a small molecule, respectively, are approved in the United States for patients with PKU and both have been shown to have modest benefits in a subset of patients. PALYNZIQ is approved only for adult PKU patients. KUVAN does not normalize Phe in most patients and has shown to be ineffective in patients with severe PKU. Despite treatment advances, including availability of a larger selection of medical and low protein foods and the approval of the two treatments, many patients still do not achieve the recommended daily Phe levels and are at risk of developing neurocognitive manifestations, including intellectual disability and neuropsychiatric disorders.

Several AAV gene therapy approaches are currently being tested in clinical trials in patients with PKU. However, following a single dose of AAV, antibodies are induced against the AAV capsid and thus, AAV gene therapy can only be administered once. The antibodies formed following a single dose of AAV prevent re-treatment to increase or extend efficacy for patients with inadequate initial response or declining levels of expression. Further, it precludes treatment of pediatric patients, whose organ growth and dividing cells would dilute expression over time, and therefore would require redosing. As a result, these therapies do not have the opportunity to correct PKU at or near the onset of disease, allowing for normal neurocognitive development.

Given the limitations of currently approved therapies and the AAV gene therapy approaches under development, there is a substantial unmet need for more effective therapies for PKU.

### *Our approach*

Our non-viral gene therapy approach aims to:

- achieve stable correction of Phe levels in PKU patients of all ages upon initial dose or through individualized patient dose titration, allowing them to normalize their diet, eliminate the burden of ongoing treatment and stabilizing and/or preserving neurocognitive function;
- achieve the desired level of gene expression for each patient through our ability to redose;
- treat patients effectively for life by episodically monitoring serum Phe levels and redosing as needed, should expression wane over time;
- reverse attention, memory or executive function deficits in adults and adolescents; and
- preserve normal neurocognitive development in infants and children.

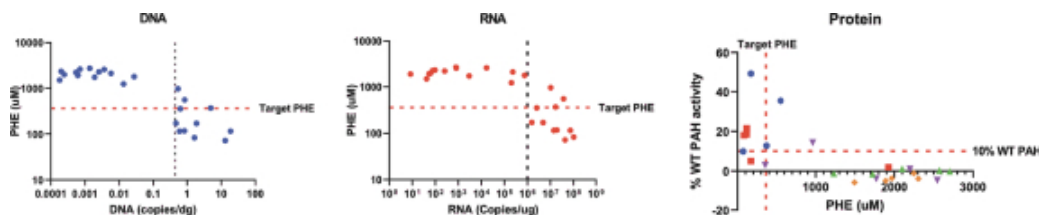
To establish benchmarks for full correction in PKU, we conducted a study utilizing the established mouse model of PKU, known as PAH<sup>enu2</sup>, a mouse model in which the PAH gene is mutated, leading to dramatically elevated Phe, to assess how many copies of ceDNA, ceDNA-derived PAH RNA and ceDNA-derived PAH protein are required for full correction in this model. In this study, we administered a ceDNA-PAH construct by hydrodynamic injection into PAH<sup>enu2</sup> mice. As shown in the figure below, we found that animals that had full correction of Phe, which is greater than 360 micromolar, or  $\mu\text{M}$ , had the following:

- ceDNA-PAH DNA copies in the liver of at least  $\sim 0.5$  copies per diploid genome, or dg;

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- ceDNA-PAH derived RNA transcripts at least  $1 \times 10^6$  copies/ $\mu\text{g}$ ; and
- ceDNA-PAH derived protein of at least 10% of normal levels.

### Threshold levels for ceDNA-PAH correction in PKU mice

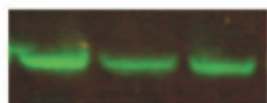


As shown in the left figure below, several ceDNA-PAH constructs express PAH protein at varying levels by Western Blot in cell culture.

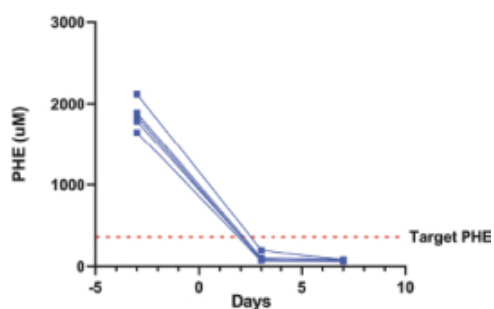
As shown in the right figure below, our most potent ceDNA-PAH construct, when administered hydrodynamically, has normalized Phe levels in PAHenu2 mice. The PAHenu2 mice serum samples at baseline exhibited very high Phe levels of greater than  $1500\mu\text{M}$ , and dropped below target Phe levels (shown by the dashed red line) at three and seven days after IV administration of ceDNA-PAH.

### Expression of ceDNA-PAH *in vitro* and correction of Phe after hydrodynamic injection of ceDNA-PAH *in vivo*

#### Expression of ceDNA-PAH by immunoblot



#### Phenylalanine normalization after hydrodynamic injection of ceDNA-PAH in PKU mice



#### Next steps

We expect to achieve murine preclinical proof of concept in early 2021, defined as Phe normalization in PAHenu2 in mice after administration of ceDNA-PAH formulated in ctLNP. We plan to begin IND-enabling studies in 2021 and to submit an IND application for this program in 2022.

#### Wilson disease

##### Overview

Wilson disease is a rare autosomal recessive disease due to a loss-of-function mutation in the ATB7B copper transporter. There are approximately 11,000 patients with Wilson disease in the United States and 17,000 patients

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in the European Union. Mutations in the ATP7B copper transporter prevent incorporation of copper into ceruloplasmin and diminishes biliary secretion of copper excess, resulting in toxic accumulation of copper in the liver and brain. Clinically, liver damage begins by six years of life and then progresses with inflammation, fibrosis and joint pain. Many patients also develop CNS manifestations of copper overload, including psychosis, tremors, dysarthria, or slurred speech and muscle stiffness.

### *Current approaches and limitations*

There are no approved gene therapies for Wilson disease. Current treatment approaches include chelators promoting excretion of copper from the body and zinc salts that reduce copper absorption. These therapies have demonstrated limited effectiveness and safety issues, resulting in poor compliance in patients. The only curative option for acute liver failure related to Wilson disease today is a liver transplant, which cannot be offered to most patients due to lack of availability of matched donors. The average age of Wilson disease patients undergoing liver transplantation is 15 years old for those who have an available donor, indicating the need for intervention in childhood to prevent progression to this point.

There are no current gene therapy clinical trials for Wilson disease. The ATP7B gene is 4.4 kb, which means the size of the gene plus the remainder of the expression cassette cannot fit within an AAV. One preclinical AAV gene therapy program, known as VTX-801, is in development for Wilson disease utilizing a truncated ATP7B gene that may not have the full functionality of ATP7B.

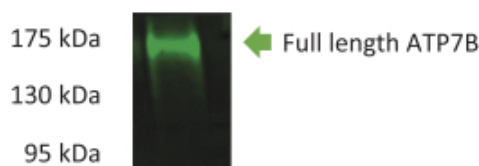
### *Our approach*

Our gene therapy approach aims to do the following:

- enable full correction of copper metabolism by broadly transducing hepatocytes and utilizing full-length ATP7B gene and an optimized expression cassette;
- achieve full hepatic correction early in the disease, re-directing copper to be incorporated into ceruloplasmin and normalizing bile excretion, thereby avoiding hepatic and CNS tissue accumulation and irreversible liver fibrosis and neurocognitive decline;
- initiate treatment in children, early in the disease, to prevent the accumulation of liver damage and irreversible neurocognitive decline;
- maintain correction of hepatocytes by redosing to compensate for the effect of injury-driven cell division in the liver;
- achieve the appropriate therapeutic level of ATP7B needed for correction using serum biomarkers via individualized patient titration at the onset of therapy; and
- maintain copper and ceruloplasmin levels in the normal range throughout life with maintenance therapy, as needed.

We have generated Wilson disease plasmid constructs and demonstrated the expression and appropriate sub-cellular location of the expressed protein *in vitro*. We have induced cells to produce the full length ATP7B protein at 157 kilodaltons using Western Blot, as shown in the figure below. We have also demonstrated, by immunohistochemistry, appropriate localization of ATP7B in the golgi apparatus around the nucleus within cells, consistent with where native ATP7B localizes.

### **ATP7B plasmid constructs result in full length ATP7B protein production *in vitro***



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### *Next steps*

We plan to begin preclinical development in 2021 for this program.

### **Gaucher disease, Type 1**

#### *Overview*

Gaucher disease is a rare inherited autosomal recessive disorder caused by the insufficient expression of lysosomal enzyme glucocerebrosidase, or GCase. Gaucher disease is the most common inherited lysosomal storage disease. There are approximately 6,000 patients with Gaucher disease in the United States and 9,000 patients in the European Union. Ninety percent of Gaucher patients are classified as Type 1, the most common form, which has no CNS involvement in the disease. Patients with Type 1 disease are typically diagnosed between 10 to 15 years of age.

Patients with Gaucher disease do not produce adequate levels of GCase, which causes glucosylceramide, a toxic lipid, to accumulate in macrophage lineage cells in visceral organs. This results in splenomegaly, hepatomegaly and cytopenia. Disease progression commonly involves loss of bone mass, either osteopenia or osteoporosis and can lead to painful bone crises and avascular necrosis, or death of bone tissue. We are specifically developing a gene therapy approach to address Type 1 Gaucher disease.

#### *Current approaches and limitations*

The current standard of care for Gaucher disease includes enzyme replacement therapy, or ERT, for patients of all ages or substrate reduction therapy, or SRT, for adults with Type 1. ERT is recommended as a potentially suitable treatment for all symptomatic Type 1 patients, though the required IV infusions every two weeks can lead to difficult treatment burden.

SRT treats Gaucher disease by inhibiting cellular production of glucosylceramide, rather than increasing the degradation of glucosylceramides through ERT. ZAVESCA (miglustat) and CERDELGA (eliglustat) effectively treat hepatosplenomegaly in a similar time course to ERT, though improvement in hematological aspects of the disease takes longer to materialize. SRT does not correct the fundamental lack of GCase and biochemical and tissue abnormalities persist.

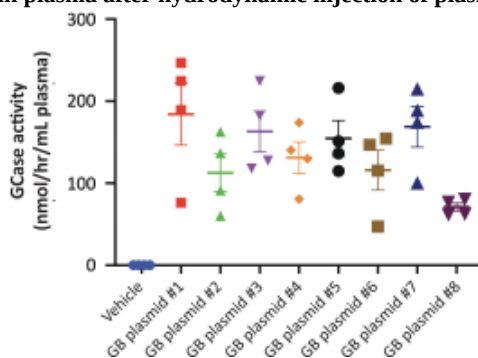
#### *Our approach*

Our gene therapy approach aims to:

- provide continuous therapeutic levels of GCase in serum and tissues that can break down glucosylceramide, which may enhance tissue correction over episodic ERT;
- administer ceDNA-GCase early in disease before the onset of inflammation, fibrosis and irreversible tissue injury;
- achieve the appropriate GCase levels for potential disease modification using biomarkers such as glucosylsphingosine, or Lyso-Gb1, via individualized patient titration;
- treat patients for life by maintaining Lyso-Gb1 levels in the normal range through redosing as needed; and
- reduce immune reactions to GCase, which occur in 2% to 15% of Gaucher patients.

We have created multiple distinct GCase plasmid constructs and have tested them for activity *in vivo*. These constructs differ in various expression cassette elements, including promoter, intron, UTR and codon optimization expression elements. We administered these plasmid GCase constructs hydrodynamically into mice and measured GCase enzymatic activity in the serum. As shown in the figure below, many of our GCase plasmid constructs have exhibited functional GCase activity in serum, indicating that hepatocytes are not only able to produce the GCase, but can also secrete it for uptake by other tissues that are affected in Gaucher.

### Detection of GCCase in plasma after hydrodynamic injection of plasmid constructs *in vivo*



#### Next steps

We plan to begin preclinical development in 2021 for this program.

#### Antibody gene therapy

##### Overview

We plan to advance product candidates to deliver antibody genes to direct the liver to express and secrete antibodies. Monoclonal antibodies, or mAbs, have demonstrated therapeutic benefit in many areas, including infectious diseases, rheumatology, hematology and oncology.

We believe that utilizing the patient’s own cells to produce and secrete therapeutic mAbs, fragments or derivatives is a potentially transformative approach that can result in greater efficacy, produced at a larger scale and with lower cost of goods compared to the passive administration of some mAbs. This approach is called antibody gene therapy, or AGT.

##### Current approaches and limitations

The cost of goods, the burden of frequent administration and the manufacturing scale limitations of mAb therapy preclude their widespread utilization in many diseases.

##### Our approach

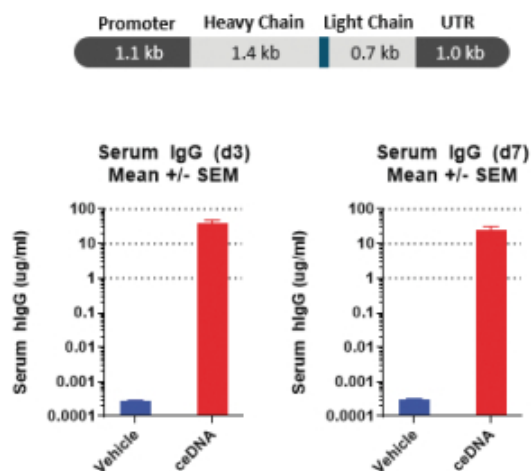
Our gene therapy approach aims to:

- enable a patient’s own body to sustainably produce and secrete a therapeutic mAb from the liver by introducing ceDNA-AGT;
- enable continuous production of protein, resulting in a stable, effective levels of serum mAb, thereby avoiding toxicity due to off-target effects of pulsatile delivery and/or loss of efficacy often associated with rapid reduction in concentrations when delivered passively;
- rapidly induce a therapeutic effect due to liver production of the therapeutic mAb within days of administration;
- potentially eliminate compliance risk due to sustained expression after a single dose;
- encode multiple mAbs on a single ceDNA construct for broad therapeutic application;
- achieve the appropriate mAb levels in the blood via individualized patient titration; and
- induce rapid onset, durable immunity via expression of mAbs to prevent infection for large populations.



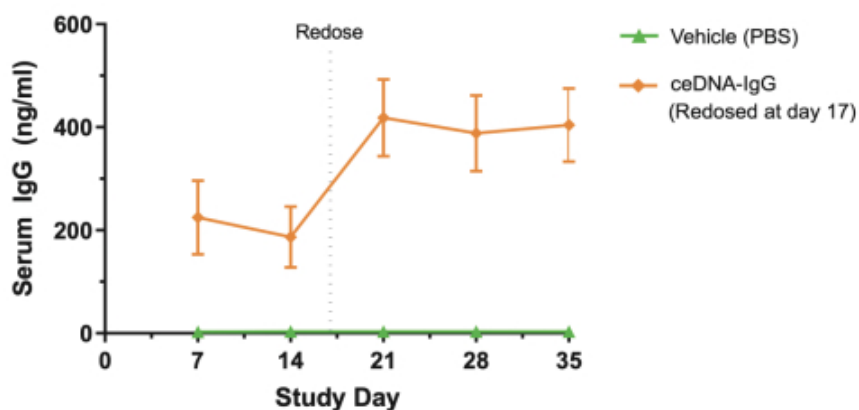
We have demonstrated hepatic expression of antibodies with ceDNA-AGT. As shown in the figure below, hydrodynamic injection of ceDNA-AGT resulted in serum mAb levels of greater than 40.0 µg/ml. Since many therapeutic mAbs are effective at serum concentrations of 1.0 to 5.0 µg/ml, we believe the level of mAb expression observed with our ceDNA-AGT is likely to be therapeutically relevant in humans.

### Hydrodynamic injection of ceDNA-AGT results in serum levels up to 40.0µg/ml



We have also demonstrated stacking of mAb expression after repeat dosing via hydrodynamic injection, as shown in the figure below.

### mAb expression increases after repeat dosing via hydrodynamic injection



### Next steps

We are advancing our initial AGT program for the treatment of an infectious disease and we are evaluating ceDNA constructs that express neutralizing mAbs targeting a surface protein for a variety of infectious agents, including hepatitis B virus, or HBV, HIV and respiratory syncytial virus, or RSV, and plan to demonstrate expression in the liver in preclinical studies in 2021. Separately, we have established a research collaboration

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with Vir Biotechnology, Inc. to explore the potential for our non-viral gene therapy platform to extend the duration and reach of Vir's mAb therapies against the SARS-CoV-2 coronavirus.

### ***Retinal diseases***

Approximately 200 million individuals suffer from inherited retinal diseases, in which a gene mutation leads to degeneration of the retina. Many of these diseases are caused by genes too large to be enclosed within AAV, including LCA10 and Stargardt disease. Current AAV gene therapy approaches are not able to encode and deliver large genetic payloads and cannot provide the full gene required to treat LCA10 and Stargardt disease. We believe using ceDNA to deliver large gene payloads efficiently and specifically to relevant cell types in the retina, with the opportunity to optimize ctLNP for minimally invasive routes of delivery, represents an important therapeutic approach.

### ***Lebers Congenital Amaurosis Type 10 (LCA10)***

#### *Overview*

LCA10 is the most common genetic cause of childhood vision loss. There are approximately 2,200 patients with LCA10 in the United States and 3,400 patients in the European Union. It is a severe, autosomal recessive retinal dystrophy due to a mutation in the CEP290 protein that is expressed in and required for proper functioning of retinal photoreceptors. LCA10 causes blindness or severe vision loss, often from birth or within the first year of life.

#### *Current approaches and limitations*

There are no approved therapies for LCA10. Several therapeutic programs are in clinical development for LCA10, including a splicing oligonucleotide given episodically by intravitreal injection and a gene editing approach. Both approaches address only a subset of LCA10 patients, specifically those with a CEP290 mutation amenable to splicing alteration, which makes up approximately 60% of the population. CEP290 is a large gene of 7.4 kb, which exceeds the 4.7 kb payload capacity of AAV. No single approach has been able to address the many mutations that cause LCA10.

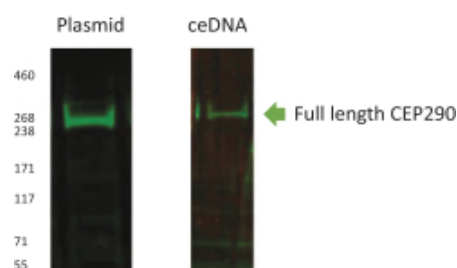
#### *Our approach*

Our gene therapy approach aims to:

- deliver directly to the retina;
- treat patients irrespective of their CEP290 mutation;
- utilize ctLNP to specifically deliver CEP290 to photoreceptors and not to retinal glial and immune cells, thereby potentially increasing the safety, tolerability and durability of transgene expression;
- enable single-dose therapy delivered subretinally, which may increase efficacy and compliance when compared, for example, to episodic intravitreal delivery; and
- treat infants and children to halt further decline of and restore vision.

We have created multiple plasmid and ceDNA constructs encoding the CEP290 gene and have demonstrated expression of full-length protein after transfection in cells in culture, as shown in the figure below.

### Plasmid and CEP290 express full-length protein in HEK293 cells *in vitro*



#### *Next steps*

We plan to begin preclinical development in 2021 for this program.

#### **Stargardt disease**

##### *Overview*

Stargardt disease is the most common inherited macular dystrophy. There are approximately 37,000 patients with Stargardt disease in the United States and 66,000 patients in the European Union. Stargardt disease is an autosomal recessive disease due to mutation in the ABCA4 gene that is expressed in both the RPE and retinal photoreceptors. Loss of ABCA4 function disrupts normal processing of retinaldehyde, or Vitamin A, in both photoreceptors and RPE cells leading to accumulation of toxic bis-retinoid byproducts and photoreceptor death. Patients usually present in childhood with loss of visual acuity and exhibit progressive loss of RPE and photoreceptor cells.

##### *Current approaches and limitations*

There are currently no proven treatments for Stargardt disease. The ABCA4 gene is approximately 6.7 kb, too large to be delivered by AAV. There are currently no ongoing gene therapy trials for Stargardt disease. The goal of therapy in Stargardt disease is to preserve vision by correcting ABCA4 expression in enough photoreceptors and RPE cells to halt the progressive loss of these cells that would otherwise occur.

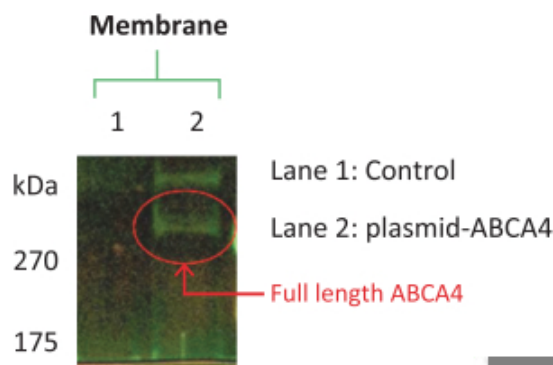
##### *Our approach*

Our gene therapy approach aims to:

- deliver to photoreceptors and RPE cells to halt progressive loss in cells and preserve vision;
- protect photoreceptors and RPE cells through expression of normal ABCA4, resulting in clearance of bis-retinoid byproducts;
- drive the appropriate level of ABCA4 expression in photoreceptors and RPE cells utilizing a native ABCA4 promoter and native regulation of expression;
- maintain normal macular vision and visual acuity when given to earlier-diagnosed patients; and
- deliver the entire ABCA4 gene in a single gene therapy vector, thereby increasing efficacy relative to dual AAV approaches.

We have generated plasmid constructs that express full length ABCA4. Further, as shown in the figure below, when we fractionate cellular lysates into cytosolic and membrane compartments, we see that plasmid ABCA4 expresses appropriately in the membrane bound subcellular compartment. This is important because ABCA4 is expressed in the cellular membrane of photoreceptors. Its cellular function requires that it be expressed and also appropriately trafficked to the correct intracellular compartment. The red circle in the figure below highlights the ABCA4 protein localized within cellular membrane.

### Expression and appropriate subcellular localization of plasmid ABCA4 in vitro



#### Next steps

We plan to begin preclinical development in 2021 for this program.

### **Wet age-related macular degeneration (Wet AMD)**

#### Overview

Age-related macular degeneration, or AMD, is the leading cause of irreversible vision loss occurring in approximately 10 million people in the United States. Wet AMD is the most severe form, characterized by neovascularization of the retina, leading to significant loss in visual acuity and rapid progression to blindness. There are approximately 1.2 million patients with wet AMD in the United States and over 2.5 million patients in the European Union. Wet AMD is most common in individuals over the age of 50, with increasing incidence every decade thereafter.

#### Current approaches and limitations

Passive administration of anti-vascular endothelial growth factor, or anti-VEGF, mAbs are an established therapy for patients with wet AMD. Anti-VEGF therapy, such as EYLEA (aflibercept), is effective in slowing the loss of visual acuity in patients with wet AMD. However, the frequency of intravitreal administration is a barrier to adherence and to widespread adoption.

AAV gene therapy to establish intra-ocular expression of anti-VEGF molecules is in early clinical development, either by subretinal or intravitreal delivery. It is unclear today if these therapies will generate sufficient expression of anti-VEGF in the retina. If successful, the scale limitations of AAV may present additional challenges to providing therapy for a substantial proportion of wet AMD patients.

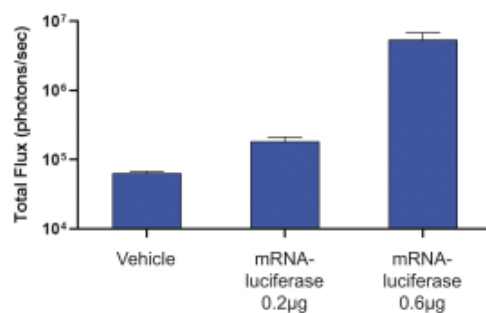
#### Our approach

Our gene therapy approach aims to:

- deliver intravitreally to enable retinal cells to express and secrete an anti-VEGF molecule;
- provide a durable and sustained level of expression of anti-VEGF, which may enhance regression of neovascularization and improve visual acuity and may enable administration only a few times over the life of a patient; and
- define when repeat therapy would be indicated to optimally preserve the retina.

In order to establish a baseline for the biodistribution of ctLNP in the eye, we administered mRNA-luciferase intravitreally at two doses of 0.2 $\mu$ g and 0.6 $\mu$ g using our ctLNP delivery system. As shown in the figure below, this resulted in luciferase expression in the retina.

### Expression after intravitreal administration of mRNA-luciferase using ctLNP



We have generated several anti-VEGF mAb ceDNA constructs and have shown that these constructs result in high levels of anti-VEGF mAb levels in the blood after hydrodynamic intravenous delivery.

#### *Next steps*

We aim to combine these constructs with ctLNP to achieve intravitreal delivery of relevant antibody levels in the retina. We plan to begin preclinical development in 2021 for this program.

#### *Expansion opportunities in other tissues*

We plan to expand our portfolio by pursuing additional programs in rare and prevalent diseases of the skeletal muscle, oncology and the CNS by developing discrete ctLNPs, each engineered to reach a specific tissue.

#### *Skeletal muscle*

There are a variety of genetic muscle disorders, including muscular dystrophies, that may be treated by efficient and systemic gene therapy to skeletal muscle. We are currently developing a ctLNP utilizing a targeting ligand to deliver ceDNA specifically to skeletal muscle.

We believe this approach would have several benefits for rare monogenic diseases of the skeletal muscle, including:

- early treatment, near the onset of disease, before inflammation and fibrosis progressively replace muscle fibers;
- delivery of full-length of defective skeletal muscle genes, which are often very large as is the case, for example, for dystrophin, the gene responsible for Duchenne Muscular Dystrophy, or DMD, and genes that form the sarcoglycan complex, which are responsible for various forms of limb-girdle muscular dystrophy;
- efficient delivery of the gene of interest to enough muscle fibers to change the course of disease;
- sufficient expression within transduced muscle fibers to allow for normal constitution of the skeletal muscle fibers during growth and development; and
- keeping up with patients' needs over time through redosing.

We believe there are many diseases in the skeletal muscle with unmet need such as DMD, myotonic dystrophy, limb girdle dystrophies and fascioscapulohumeral dystrophies, which we may pursue in the future.

#### *CNS*

We plan to explore the use of ceDNA to correct disorders of the CNS. The work we are doing with local delivery in the retina to photoreceptors may inform expansion into the CNS, beginning for example with focal epilepsies, in which expression of a novel gene within a specific region of neurons may stop the abnormal seizures. One

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such example is Dravet syndrome, an epilepsy disorder that begins in infancy or early childhood usually caused by a loss-of-function mutation in the SCN1A gene. Another example is MPSII, or Hunter syndrome, which is caused by a deficiency in iduronate sulfatase resulting in both somatic (liver, bone and visceral organs) and CNS accumulation of toxic glycosaminoglycans.

### ***Oncology***

We plan to develop the use of ceDNA to treat a variety of cancer indications. We believe that we can use distinct targeting ligands to deliver ceDNA specifically and efficiently to tumors and can utilize ceDNA to express high levels of relevant proteins within the tumor. For example, we believe after systemic delivery and efficient uptake by tumors, the expression of checkpoint inhibitors and particular cytokines encoded by the ceDNA may have both direct anti-tumor activity and may stimulate the immune system to respond to and attack tumor cells. Many of the genes that we can express within tumors have limited efficacy and substantial safety and tolerability issues when given systemically. The key attribute of this approach is the ability to drive efficient and selective uptake of ceDNA within tumors and then local, high concentrations of relevant anti-tumor agents.

### ***Manufacturing***

We have personnel with extensive technical, manufacturing, analytical and quality experience to oversee all internal and contracted manufacturing and testing activities. Relying on these personnel, we have built development laboratories to produce ceDNA (drug substance) and lipid nanoparticle-encapsulated ceDNA (drug product) for use in our research activities. We have produced ceDNA drug substance at up to 200 liters at our CDMOs. We routinely manufacture drug product through our ctLNP manufacturing process to support our research studies. We plan to use our CDMOs to support our IND-enabling studies and to fully supply our clinical trials and commercial activities. As we scale manufacturing, we intend to continue to expand and strengthen our network of CDMOs, and we will also consider investing in internal cGMP manufacturing capabilities and infrastructure in the future if there is a technical need or a strategic or financial benefit.

Manufacturing is subject to extensive regulations that impose procedural and documentation requirements. These regulations govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance. Our systems and contractors are required to comply with these regulations and are assessed through regular monitoring and formal audits.

### ***Drug substance***

We believe that the ceDNA drug substance requirements for our programs can be met by a variety of domestic and international contractors with standard biological manufacturing equipment. We have established a cGMP-ready process at the 200-liter scale, which we have transferred to our drug substance CDMOs to supply ceDNA drug substance for IND-enabling studies, clinical trials and early commercial activities. To ensure supply chain continuity, we have also established service agreements with additional suppliers to afford redundancy and flexibility in scaling. We have access rights to a biologics facility at one of our CDMOs that we believe could fully support multiple clinical programs if and when we advance our programs into clinical trials, as well as the early phases of commercialization.

We have invested in technical expertise and internal capabilities to optimize and develop the ceDNA drug substance process and to provide technical management and quality oversight for our process transfers to CDMOs.

Future ceDNA drug substance processes may require additional manufacturing capabilities, which may be addressed by either expanding our capabilities with existing contractors or establishing manufacturing supply relationships with new contract manufacturers. These changes in processes may also require new supply chain agreements with CDMOs that specialize in raw material manufacturing.

### ***Drug product***

Our drug product is ceDNA formulated with ctLNP. We believe that our drug product requirements can be met by a variety of domestic and international CDMOs. We have selected a subset of experienced organizations familiar with the specific operations that our current drug product processes require. We have established a service agreement with one of these CDMOs and have also engaged with suppliers for key components of our ctLNP delivery system.

We have invested in technical expertise and internal capabilities to optimize and develop the drug product process and to provide technical management and quality oversight for our process transfers to CDMOs. We have transitioned our drug product process from research-scale using microfluidics to standard clinical-scale equipment supporting cGMP operations for other established LNP-based modalities. These scaled systems have generated representative and well-characterized drug product that we have used in our preclinical studies. Additionally, as with our drug substance processes, progress on analytics has allowed us to leverage insights into our delivery system to upgrade and characterize purity and homogeneity. We plan to continue to implement process changes to improve purity and yield.

### ***Intellectual property***

We strive to protect our proprietary technology, inventions, improvements, platforms, product candidates and components thereof, their methods of use and processes for their manufacture that we believe are important to our business, including by obtaining, maintaining, defending and enforcing patent and other intellectual property rights for the foregoing in the United States and in certain foreign jurisdictions. We also rely on trade secrets and confidentiality agreements to protect our confidential information and know-how and other aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success depends in part on our ability to:

- obtain, maintain, enforce and defend patent and other intellectual property rights for our commercially important technology, inventions and improvements;
- preserve the confidentiality of our trade secrets and other confidential information;
- obtain and maintain licenses to use and exploit intellectual property owned or controlled by third parties;
- operate without infringing, misappropriating or otherwise violating any valid and enforceable patents and other intellectual property rights of third parties; and
- defend against challenges and assertions by third parties challenging the validity or enforceability of our intellectual property rights, or our rights in our intellectual property, or asserting that the operation of our business infringes, misappropriates or otherwise violates their intellectual property rights.

### ***Patent portfolio***

As of December 31, 2020, we own approximately 40 patent application families related to our business, including 11 pending Patent Cooperation Treaty, or PCT, patent applications and eight PCT applications that have entered the national stage in the United States and certain foreign jurisdictions, including Europe and Japan (one of which is jointly owned with UMass), and we exclusively license one patent application family, which has entered the national stage in the United States and certain foreign jurisdictions, including Europe and Japan. We also non-exclusively license one patent application family, which includes issued patents in each of the United States, Australia and Israel and national stage patent applications in several other jurisdictions, including Europe and Japan. In addition, we own approximately 22 U.S. provisional patent applications within the priority year. We do not currently own or exclusively license any issued patents covering any of our programs or technology, including the ceDNA platform, ctLNP delivery system and manufacturing processes. Our owned and licensed patent applications cover various aspects of our programs and technology, including our ceDNA construct, ctLNP delivery system and manufacturing process as further described below. Any U.S. or foreign patents issued from national stage filings of our owned or exclusively in-licensed PCT patent applications and any U.S. patents

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issued from non-provisional applications we may file in connection with our provisional patent applications would be scheduled to expire on various dates from 2037 through 2041, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

### *ceDNA construct*

As of December 31, 2020, we own approximately 28 patent application families, including four pending PCT patent applications and six PCT applications that have entered the national stage in a number of jurisdictions outside the United States (one of which is jointly owned with UMass), and we exclusively license from UMass and Voyager one patent application family, which has entered the national stage in the United States and other jurisdictions, including Europe and Japan. These patent applications cover various aspects of our ceDNA construct, including ceDNA construct variants, certain disease-targeted ceDNA compositions and methods of use. We have also non-exclusively licensed one patent application family from the NIH and the Institut de Myologie, Universite Pierre et Marie Curie, Centre National de la Recherche Scientifique and Inserm Transfert SA, which we refer to as the French Institutions, which includes issued patents in each of the United States, Australia and Israel and national stage patent applications in other jurisdictions, including Europe and Japan, which cover our ceDNA construct, certain disease-targeted ceDNA compositions and methods of use. In addition, we own approximately 19 U.S. provisional patent applications within the priority year, which cover ceDNA construct variants, general applications of the ceDNA construct technology and certain properties of the construct, specific disease-targeted ceDNA compositions and methods of use. Any U.S. or foreign patents issued from the pending U.S. or foreign non-provisional patent applications or from non-provisional applications we may file in connection with the pending provisional patent applications would be scheduled to expire on various dates from 2038 through 2041, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

### *ctLNP delivery system*

As of December 31, 2020, we own approximately 10 patent application families, including six pending PCT patent applications and one PCT application that has entered the national stage in the United States and a number of jurisdictions outside the United States, and approximately three U.S. provisional patent applications within the priority year with respect to our ctLNP delivery system, including certain lipid and lipid nanoparticle compositions and combinations with ceDNA and/or targeting agents and methods of use. Any U.S. or foreign patents issued from the pending U.S. or foreign non-provisional patent applications or from any non-provisional applications we may file in connection with these provisional patent applications would be scheduled to expire on various dates from 2038 through 2041, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

### *Manufacturing processes*

As of December 31, 2020, we own approximately two patent application families, including one pending PCT patent application and one PCT application that has entered the national stage in the United States and a number of jurisdictions outside the United States, with respect to our ceDNA manufacturing processes. Any U.S. or foreign patents issued from the pending U.S. or foreign non-provisional patent applications or from any non-provisional applications we may file in connection with these provisional patent applications would be scheduled to expire on various dates from 2039 through 2040, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

### **Patent prosecution**

A PCT patent application is not eligible to become an issued patent until, among other things, we file one or more national stage patent applications within 30 months, 31 months or 32 months of the PCT application's priority date, depending on the jurisdiction, in the countries in which we seek patent protection. If we do not



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timely file any national stage patent applications, we may lose our priority date with respect to our PCT patent application and any potential patent protection on the inventions disclosed in such PCT patent application. Moreover, a provisional patent application is not eligible to become an issued patent. A provisional patent application may serve as a priority filing for a non-provisional patent application we file within 12 months of such provisional patent application. If we do not timely file non-provisional patent applications, we may lose our priority date with respect to our existing provisional patent applications and any potential patent protection on the inventions disclosed in our provisional patent applications.

While we intend to timely file additional provisional patent applications and national stage and non-provisional patent applications relating to our PCT patent applications, we cannot predict whether any of our patent applications will result in the issuance of patents. If we do not successfully obtain patent protection, or if the scope of the patent protection we or our licensors obtain with respect to our product candidates or technology, including our ceDNA constructs, ctLNP delivery system or manufacturing processes is not sufficiently broad, we will be unable to prevent others from using our technology or from developing or commercializing technology and products similar or identical to ours or other similar competing products and technologies. Our ability to stop third parties from making, using, selling, offering to sell, importing or otherwise commercializing any of our technology, inventions and improvements, either directly or indirectly, will depend in part on our success in obtaining, maintaining, defending and enforcing patent claims that cover our technology, inventions and improvements.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. The protection afforded by a patent varies on a product-by-product basis, from jurisdiction-to-jurisdiction, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of patent term adjustments and regulatory-related patent term extensions, the availability of legal remedies in a particular jurisdiction and the validity and enforceability of the patent. No consistent policy regarding the scope of patent claims allowable in the field of genetic therapy has emerged in the United States. Moreover, patent laws and related enforcement in various jurisdictions outside of the United States are uncertain and may not protect our rights to the same extent as the laws of the United States. Changes in the patent laws and rules, whether by legislation, judicial decisions or regulatory interpretation, in the United States and other jurisdictions may diminish our ability to protect our inventions and obtain, maintain, defend and enforce our patent rights, and could therefore affect the value of our business.

The area of patent and other intellectual property rights in biotechnology is evolving and has many risks and uncertainties, and third parties may have blocking patents and other intellectual property that could be used to prevent us from commercializing our platforms and product candidates and practicing our proprietary technology. Our patent rights may be challenged, narrowed, circumvented, invalidated or ruled unenforceable, which could limit our ability to stop third parties from marketing and commercializing related platforms or product candidates or limit the term of patents that cover our platforms and product candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against third parties with similar technology, and third parties may independently develop similar technologies. Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any competitive advantage provided by the patent. For this and other risks related to our proprietary technology, inventions, improvements, platforms and product candidates and intellectual property rights related to the foregoing, please see the section entitled “Risk factors—Risks related to our intellectual property.”

### ***Patent term extensions***

The term of individual patents depends upon the laws of the jurisdictions in which they are obtained. In most jurisdictions in which we file, the patent term is 20 years from the earliest date of filing of the first non-provisional patent application to which the patent claims priority. However, the term of U.S. patents may be extended or adjusted for delays incurred due to compliance with FDA requirements or by delays encountered

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during prosecution that are caused by the United States Patent and Trademark Office, or the USPTO. For example, in the United States, a patent claiming a new biologic product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, for up to five years beyond the normal expiration date of the patent. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. For more information on patent term extensions, see "Business—Government regulation—Patent term restoration and extension". In the future, if and when any product candidates we may develop receive FDA approval, we expect to apply for patent term extensions on issued patents covering those product candidates. Moreover, we intend to seek patent term adjustments and extensions for any of our issued patents in any jurisdiction where such adjustments and extensions are available. However, there is no guarantee that the applicable authorities, including the USPTO and FDA, will agree with our assessment of whether such adjustments and extensions should be granted, and even if granted, the length of such adjustments and extensions.

### ***Trade secrets***

In addition to patent protection, we also rely on trade secrets, know-how, unpatented technology and other proprietary information to strengthen our competitive position. We take steps to protect and preserve our trade secrets and other confidential and proprietary information and prevent the unauthorized disclosure of the foregoing, including by entering into non-disclosure and invention assignment agreements with parties who have access to our trade secrets or other confidential and proprietary information, such as employees, consultants, outside scientific collaborators, contract research and manufacturing organizations, sponsored researchers and other advisors, at the commencement of their employment, consulting or other relationships with us. In addition, we take other appropriate precautions, such as maintaining physical security of our premises and physical and electronic security of our information technology systems, to guard against any misappropriation or unauthorized disclosure of our trade secrets and other confidential and proprietary information by third parties.

Despite these efforts, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or other confidential or proprietary information. In addition, we cannot provide any assurances that all of the foregoing non-disclosure and invention assignment agreements have been duly executed, and any of the counterparties to such agreements may breach them and disclose our trade secrets and other confidential and proprietary information. Although we have confidence in the measures we take to protect and preserve our trade secrets and other confidential and proprietary information, they may be inadequate, our agreements or security measures may be breached, and we may not have adequate remedies for such breaches. Moreover, to the extent that our employees, contractors, consultants, collaborators and advisors use intellectual property owned by others in their work for us, disputes may arise as to our rights in any know-how or inventions arising out of such work. For more information, please see the section entitled "Risk factors—Risks related to our intellectual property."

### ***License agreements***

We are a party to a number of license agreements under which we license patents, patent applications and other intellectual property from third parties. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future. We consider the following license agreements to be material to our business.

#### *License agreement with the National Institutes of Health*

In February 2017, we entered into a license agreement with the NIH, which was amended in July 2019 to include the French Institutions as licensors. Pursuant to the amended agreement, or the NIH Agreement, NIH and the

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French Institutions granted us a worldwide, non-exclusive license under a patent application family related to our ceDNA construct. This patent application family includes national stage patent applications in jurisdictions outside the United States, including Europe and Japan, and issued patents in each of the United States, Australia and Israel. The issued patents and any future patents issued from the pending patent applications would be scheduled to expire on various dates from March 2032 through October 2032, without taking into account any possible extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees. The non-exclusive license confers the right to make and have made, research and have researched, use and have used, sell and have sold, offer to sell and import products and to practice processes, in each case, covered by the licensed patents and patent applications, for the treatment, prevention or palliation of any human disease or condition.

Under the NIH Agreement, we are obligated to use reasonable commercial efforts to ensure that the licensed products and processes are utilized and made available to the public on reasonable terms, including pursuing commercially reasonable broad international patient accessibility for licensed gene therapy products for the treatment of rare diseases, in accordance with an agreed upon commercial development plan for gene therapy-based human therapeutics and certain performance milestone events. Unless terminated earlier, the NIH Agreement remains in effect until the last to expire of the licensed patent rights on a licensed product-by-licensed product and country-by-country basis. NIH and the French Institutions may terminate the NIH Agreement if we fail to perform our material obligations, including but not limited to our failure to meet the applicable performance milestones despite using commercially reasonable efforts, and have not remediated such deficiency within a specified time period. NIH and the French Institutions can terminate the NIH Agreement in the event we become insolvent, file a petition in bankruptcy, have such a petition filed against us, or determine to file a petition in bankruptcy. In addition, NIH and the French Institutions may terminate the NIH Agreement in the event of a material breach by us and failure to cure such breach within a certain period of time. We can voluntarily terminate the NIH Agreement with prior notice to NIH and the French Institutions.

As part of the NIH Agreement, we agreed to make milestone payments upon the achievement of certain milestones up to a maximum aggregate total of \$350,000 for each licensed product, as well as a low single-digit royalty on net sales of licensed products. These royalty obligations last on a licensed product-by-licensed product and country-by-country basis until the expiration of the last licensed patent rights covering such licensed product in such country. In addition, if we sublicense rights under the NIH Agreement, we are required to pay a high single-digit percent of the sublicense revenue to NIH. Additionally, under the NIH Agreement, we may be required to reimburse the French Institutions for a portion of certain past and ongoing patent related expenses, including expenses associated with the preparation, filing, prosecution and maintenance of all patents and patent applications. As of December 31, 2020, there have been no invoiced expenses related to these reimbursable costs.

### *License Agreement with the University of Massachusetts*

In June 2017, we entered into a license agreement with UMass pursuant to which UMass granted us an exclusive, worldwide license under a patent application family related to our ceDNA construct, which has pending national stage patent applications in the United States and certain foreign jurisdictions. In June 2020 Voyager became a joint owner with UMass of the licensed patent application family, and we entered into an amendment to the UMass Agreement under which UMass, on behalf of Voyager, expanded the license granted to us to include an exclusive license to Voyager's rights in the licensed patent application family, subject to Voyager's retained non-exclusive rights to practice and exploit the licensed patent application family solely for its AAV gene therapy products. Any U.S. or foreign patents issued from the pending licensed U.S. or foreign patent applications would be scheduled to expire in March 2037, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees. The exclusive license confers the right to research, develop, manufacture, have manufactured, use, offer for sale, sell and import products and practice and have practiced processes, in each case, covered by the patent application family.

Unless terminated earlier, our license agreement with UMass, as amended, which we refer to as the UMass Agreement, will continue until the last-to-expire valid claim of the licensed patents. UMass may terminate the

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UMass Agreement if we fail to perform our material obligations, including but not limited to our failure to meet the applicable performance milestones despite using commercially reasonable efforts, and have not remediated such deficiency within a specified time period or negotiated a revised performance timeline. UMass can terminate the UMass Agreement if we fail to make any payments within a specified period after receiving written notice of such failure, or in the event of a material breach by us and failure to cure such breach within a certain period of time, provided that, if we fail to make payments due under the UMass Agreement more than a certain number of times, UMass may terminate the agreement immediately without any cure period. We can voluntarily terminate the UMass Agreement with prior notice to UMass.

Under the UMass Agreement, we agreed to use diligent efforts to develop the licensed products and introduce them into the commercial market and make them reasonably available to the public thereafter. Specifically, we agreed to achieve regulatory approval for and commercially launch at least one licensed product in the U.S. by certain specified dates.

As part of the UMass Agreement, we have issued to UMass 125,677 shares of our common stock. In addition, we may be obligated to make milestone payments up to \$1,143,750 per licensed product that are contingent upon the achievement of certain regulatory and commercialization milestones, as well as low single-digit royalties on net sales of licensed products on a licensed product-by-licensed product and country-by-country basis. If we sublicense our rights under the UMass Agreement, we are required to pay a low-to-mid single-digit percentage of the license revenue to UMass, which will vary depending on when the sublicense agreement to a third party was executed. Royalty obligations under the UMass Agreement will continue until the expiration of the last valid claim of a licensed patent covering such licensed product in such country. As of December 31, 2020, we have recorded no royalty or milestone liabilities under the UMass Agreement.

### **Competition**

The biotechnology and biopharmaceutical industries generally, and the genetic medicine field specifically, are characterized by rapid evolution of technologies, sharp competition and strong defense of intellectual property. Any product candidates that we successfully develop and commercialize will have to compete with existing therapies and new therapies that may become available in the future. While we believe that our technology, development experience and scientific knowledge in the field of gene therapy, nucleic acid delivery and manufacturing provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions.

There are numerous companies that are selling or developing genetic medicines, including in indications for which we may develop our non-viral gene therapies. These companies include viral gene therapy companies such as BioMarin Pharmaceuticals, Inc., Homology Medicines, Inc., Adverum Biotechnologies, Inc., Ultragenyx Pharmaceutical Inc. and Hoffmann La Roche Ltd; gene editing companies such as CRISPR Therapeutics AG, Intellia Therapeutics, Inc., and Editas Medicine, Inc.; and mRNA companies such as Moderna, Inc.

Many of our competitors, either independently or with strategic partners, have substantially greater financial, technical and human resources than we do. Accordingly, our competitors may be more successful than we are in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approval for treatments and achieving widespread market acceptance. Merger and acquisition activity in the biotechnology and biopharmaceutical industries may result in resources being concentrated among a smaller number of our competitors. These companies also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials and acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Our commercial opportunity could be substantially limited if our competitors develop and commercialize products that are more effective, safer, less toxic, more convenient or less expensive than products we may

develop. In geographies that are critical to our commercial success, competitors may also obtain regulatory approvals before us, resulting in our competitors building a strong market position in advance of the entry of our products. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of other drugs. The key competitive factors affecting the successful of all any products we may develop are likely to be their efficacy, safety, convenience, price and availability of reimbursement.

### **Government regulation**

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

### ***Licensure and regulation of biologics in the United States***

In the United States, any product candidates we may develop would be regulated as biological products, or biologics, under the Public Health Service Act, or PHS Act, and the Federal Food, Drug and Cosmetic Act, or FDCA, and its implementing regulations and guidance. The failure to comply with the applicable U.S. requirements at any time during the product development process, including preclinical testing, clinical testing, the approval process, or post-approval process, may subject an applicant to delays in the conduct of the study, regulatory review and approval and/or administrative or judicial sanctions.

An applicant seeking approval to market and distribute a new biologic in the United States generally must satisfactorily complete each of the following steps:

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practices, or GLP regulations;
- completion of the manufacture, under cGMP conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical and stability testing;
- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current Good Clinical Practices, or GCP;
- preparation and submission to the FDA of a BLA for a biologic product requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product in clinical development and proposed labelling;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, at which the product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the preclinical studies and clinical trial sites to assure compliance with GLP, as applicable, and GCP, and the integrity of clinical data in support of the BLA;

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- payment of user Prescription Drug User Fee Act, or PDUFA, securing FDA approval of the BLA and licensure of the new biologic product; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and any post-approval studies or other post-marketing commitments required by the FDA.

### *Preclinical studies and investigational new drug application*

Before testing any biologic product candidate in humans, including a gene therapy product candidate, the product candidate must undergo preclinical testing. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as studies to evaluate the potential for efficacy and toxicity in animal studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application.

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin or recommence.

As a result, submission of the IND may result in the FDA not allowing the trials to commence or allowing the trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the IND review process, it may choose to impose a partial or complete clinical hold. Clinical holds are imposed by the FDA whenever there is concern for patient safety, may be a result of new data, findings, or developments in clinical, preclinical and/or chemistry, manufacturing and controls or where there is non-compliance with regulatory requirements. This order issued by the FDA would delay either a proposed clinical trial or cause suspension of an ongoing trial, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed. This could cause significant delays or difficulties in completing our planned clinical trial or future clinical trials in a timely manner.

Additionally, gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the NIH also are potentially subject to review by a committee within the NIH's Office of Science Policy called the Novel and Exceptional Technology and Research Advisory, or the NExTRAC. As of 2019, the charter of this review group has evolved to focus public review on clinical trials that cannot be evaluated by standard oversight bodies and pose unusual risks. With certain gene therapy protocols, FDA review of or clearance to allow the IND to proceed could be delayed if the NExTRAC decides that full public review of the protocol is warranted.

### *Expanded access to an investigational drug for treatment use*

Expanded access, sometimes called "compassionate use," is the use of investigational products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational products for patients who may benefit from investigational therapies. FDA regulations allow access to investigational products under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the investigational product under a treatment protocol or treatment IND application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine

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suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act, or Cures Act, passed in 2016, if a sponsor has a policy regarding how it responds to expanded access requests, it must make that policy publicly available. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 trial; or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy, or RMAT.

In addition, 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 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 manufacturer to make its investigational products available to eligible patients as a result of the Right to Try Act.

### *Human clinical trials in support of a BLA*

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease or condition to be treated under the supervision of a qualified principal investigator in accordance with GCP requirements. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, inclusion and exclusion criteria, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

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

Further, each clinical trial must be reviewed and approved by an IRB either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, the safety of human subjects, and the possible liability of the institution. An IRB must operate in compliance with FDA regulations. The FDA, IRB, or the clinical trial sponsor may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or that the participants are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board, or DSMB. This group may recommend

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continuation of the trial as planned, changes in trial conduct, or cessation of the trial at designated check points based on certain available data from the trial to which only the DSMB has access.

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

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

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

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

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

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.



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Information about applicable clinical trials must be submitted within specific timeframes to the NIH for public dissemination on its ClinicalTrials.gov website.

### *Special regulations and guidance governing gene therapy products*

We expect that the procedures and standards applied to gene therapy products will be applied to any product candidates we may develop. The FDA has defined a gene therapy product as one that seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* prior to administration to the recipient.

Within the FDA, the Center for Biologics Evaluation and Research, or CBER, regulates gene therapy products. Within CBER, the review of gene therapy and related products is consolidated in the OTAT and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. The NIH, including the NExTRAC also advises the FDA on gene therapy issues and other issues related to emerging biotechnologies. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols.

The FDA has issued various guidance documents regarding gene therapies, including final guidance documents released in January 2020 relating to chemistry, manufacturing and controls information for gene therapy INDs, long-term follow-up after the administration of gene therapy products, gene therapies for rare diseases and gene therapies for retinal disorders, as well as draft guidance in January 2021 for Human Gene Therapy for Neurodegenerative Diseases. Although the FDA has indicated that these and other guidance documents it previously issued are not legally binding, compliance with them is likely necessary to gain approval for any gene therapy product candidate. The guidance documents provide additional factors that the FDA will consider at each of the above stages of development and relate to, among other things: the proper preclinical assessment of gene therapies; the chemistry, manufacturing and control information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe for potential delayed adverse effects in participants who have received investigational gene therapies with the duration of follow-up based on the potential for risk of such effects. For AAV vectors specifically, the FDA typically recommends that sponsors continue to monitor participants for potential gene therapy-related adverse events for up to a 5-year period.

Until 2019, most gene therapy clinical trials in the United States required pre-review by the predecessor of NExTRAC before being approved by the IRBs and any local biosafety boards or being allowed to proceed by the FDA. In 2019, the NIH substantially eliminated the pre-review process and going forward, the review of gene therapy clinical trial protocols would be largely handled by local IRBs and institutional biosafety committees, or IBCs, in addition to the FDA. Furthermore, in 2019, the NIH removed from public access the Genetic Modification Clinical Research Information System database, which previously contained substantial amounts of safety and other participant information regarding human gene therapy trials performed up to that time.

### *Pediatric Studies*

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

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric

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data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the FDA Safety and Innovation Act. The FDA maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population. In 2017, with passage of the FDA Reauthorization Act of 2017, or FDARA, Congress further modified these provisions. Previously, drugs that had been granted orphan drug designation were exempt from the requirements of the PREA. Under the amended section 505B, beginning on August 18, 2020, the submission of a pediatric assessment, waiver or deferral will be required for certain molecularly targeted cancer indications with the submission of an application or supplement to an application.

### *Compliance with cGMP requirements*

Before approving a BLA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in full compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The PHSA emphasizes the importance of manufacturing control for products like biologics whose attributes cannot be precisely defined.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Inspections must follow a “risk-based schedule” that may result in certain establishments being inspected more frequently. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA may lead to a product being deemed to be adulterated.

### *Review and approval of a BLA*

The results of product candidate development, preclinical testing and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of a BLA requesting license to market the product. The BLA must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee. Under federal law, the submission of most BLAs is subject to an application user fee, which for federal fiscal year 2021 is \$2,875,842 for an application requiring clinical data. The sponsor of a licensed BLA is also subject to an annual program fee, which for fiscal year 2021 is \$336,432. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

The FDA has 60 days after submission of the application to conduct an initial review to determine whether it is sufficient to accept for filing based on the agency’s threshold determination that it is sufficiently complete to permit substantive review. Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies agreed to by the FDA under the PDUFA, the FDA has ten months in which to complete its initial review of a standard application and respond to the applicant, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs. The review process may often be significantly extended by FDA requests for additional information or clarification.

Under the PHSA, the FDA may approve a BLA if it determines that the product is safe, pure and potent, and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure and potent. On the basis of the FDA’s evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of preclinical and clinical trial sites to assure compliance with GCPs, the FDA may issue an approval letter or a complete response

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letter, or CRL. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. If the application is not approved, the FDA will issue a CRL, which will contain the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a CRL may submit to the FDA information that represents a complete response to the issues identified by the FDA.

The FDA may also refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. In particular, the FDA may refer applications for novel biologic products or biologic products that present difficult questions of safety or efficacy to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

If the FDA approves a new product, it may limit the approved indication(s) for use of the product. It may also require that contraindications, warnings, or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's efficacy and/or safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

### *Expedited Review Programs*

The FDA is authorized to expedite the review of BLAs in several ways. Under the Fast Track program, the sponsor of a product candidate may request the FDA to designate the product for a specific indication as a Fast Track product concurrent with or after the filing of the IND application. Candidate products are eligible for Fast Track designation if they are 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 candidate and the specific indication for which it is being studied. In addition to other benefits, such as the ability to have greater interactions with the FDA, the FDA may initiate review of sections of a Fast Track application before the application is complete, a process known as rolling review.

Any product candidate submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as breakthrough therapy designation, priority review and accelerated approval.

- *Breakthrough therapy designation.* To qualify for the breakthrough therapy program, product candidates must be intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence must indicate that such product candidates may demonstrate substantial improvement on one or more clinically significant endpoints over existing therapies. The FDA will seek to ensure the sponsor of a breakthrough therapy product candidate receives intensive guidance on an efficient drug development program, intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review and rolling review.
- *Priority review.* A product candidate is eligible for priority review if it treats a serious condition and, if approved, it would be a significant improvement in the safety or effectiveness of the

treatment, diagnosis or prevention compared to marketed products. The FDA aims to complete its review of priority review applications within six months as opposed to 10 months for standard review.

- *Accelerated approval.* Drug or biologic 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. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate 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 or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.
- *Regenerative medicine advanced therapy.* With passage of the 21st Century Cures Act, or the Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is an RMAT that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate has the potential to address unmet medical needs for such disease or condition. The benefits of an RMAT designation include early interactions with the FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

None of these expedited programs change the standards for approval but they may help expedite the development or approval process of product candidates.

#### *Post-approval regulation*

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

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official lot release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of

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previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

Pharmaceutical products may be promoted only for the approved indications and in accordance with the provisions of the approved label. Although healthcare providers may prescribe products for uses not described in the drug's labeling, known as off-label uses, in their professional judgment, drug manufacturers are prohibited from soliciting, encouraging or promoting unapproved uses of a product. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

### *Orphan drug designation*

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

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

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

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same product for the same indication for seven years, except in certain limited circumstances. In particular, the concept of what constitutes the "same drug" for purposes of orphan drug exclusivity remains in flux in the context of gene therapies, and the FDA has issued recent draft guidance suggesting that it would not consider two gene therapy products to be different drugs solely based on minor differences in the transgenes or vectors within a given vector class. If a product designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a second application for a clinically superior version of the product for the same use. Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if the company with orphan drug exclusivity is not able to meet market demand or the subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or provide a major contribution to patient care. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan drug exclusivity regardless of a showing of clinical superiority. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of FDARA in 2017, but have not yet been approved or licensed by the FDA.

### *Pediatric exclusivity*

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if a BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of non-patent exclusivity that cover the product are extended by six months.

### *Biosimilars and exclusivity*

The 2010 Patient Protection and Affordable Care Act, which was signed into law in March 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. A biosimilar is a biological product that is highly similar to an existing FDA-licensed "reference product." As of January 1, 2021, the FDA has approved 29 biosimilar products for use in the United States. No interchangeable biosimilars, however, have been approved. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars. Additional guidances are expected to be finalized by the FDA in the near term.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In

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order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that 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.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law. Since the passage of the BPCIA, many states have passed laws or amendments to laws, including laws governing pharmacy practices, which are state-regulated, to regulate the use of biosimilars.

### *Federal and state data privacy and security laws*

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

Additionally, California recently enacted legislation that has been dubbed the first "GDPR-like" law in the United States. Known as the California Consumer Privacy Act, or CCPA, it creates new individual privacy rights for consumers (as that word is broadly defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA went into effect on January 1, 2020 and requires covered companies to provide new disclosures to California consumers, provide such consumers new ways to opt-out of certain sales of personal information, and allow for a new cause of action for data breaches. Additionally, effective starting on January 1, 2023, the California Privacy Rights Act, or CPRA, will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. The CCPA and CPRA could impact our business activities depending on how it is interpreted and exemplifies the vulnerability of our business to not only cyber threats but also the evolving regulatory environment related to personal data and protected health information.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that some of our current or future business activities, including certain

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

### *Patent term restoration and extension*

In the United States, a patent claiming a new biologic product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent extension of up to five years for patent term lost during product development and FDA regulatory review. Assuming grant of the patent for which the extension is sought, the restoration period for a patent covering a product is typically one-half the time between the effective date of the IND application and the submission date of the BLA, plus the time between the submission date of the BLA and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension in consultation with the FDA.

### *FDA approval of companion diagnostics*

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

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

Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations



govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution.

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the product candidate to obtain pre-market approval, or PMA, simultaneously with approval of the therapeutic product candidate. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee. For federal fiscal year 2021, the standard fee is \$365,657 and the small business fee is \$91,414.

### ***Regulation and procedures governing approval of medicinal products in the European Union***

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

#### *Clinical trial approval*

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on GCP, a system for the approval of clinical trials in the European Union has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a European Union member state in which the clinical trial is to be conducted, or in multiple member states if the clinical trial is to be conducted in a number of member states. Furthermore, the applicant may only start a clinical trial at a specific site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and corresponding national laws of the member states and further detailed in applicable guidance documents.

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, but it has not yet become effective. It will overhaul the current system of approvals for clinical trials in the European Union. Specifically, the new legislation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the European Union. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single-entry point and strictly defined deadlines for the assessment of clinical trial applications.

The conduct of all clinical trials performed in the European Union will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which ongoing clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trials Regulation becomes applicable, the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

On January 1, 2020, the website of the European Commission reported that the implementation of the new Clinical Trials Regulation was dependent on the development of a fully functional clinical trials portal and database, which would be confirmed by an independent audit, and that the new legislation would come into effect six months after the European Commission publishes a notice of this confirmation. In late 2020, the EMA indicated that it plans to focus on the findings of a system audit; improving the usability, quality and stability of the clinical trial information system; and knowledge transfer to prepare users and their organizations for the new clinical trial system. The EMA has indicated that the system will go live in December 2021.

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

### *PRIME designation in the European Union*

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

### *Marketing authorization*

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

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

Specifically, the grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of

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the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC lays down specific rules concerning the authorization, supervision and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety and efficacy of their products to EMA which provides an opinion regarding the application for marketing authorization. The European Commission grants or refuses marketing authorization in light of the opinion delivered by EMA.

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

### *Specialized procedures for gene therapies*

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

### *Pediatric Studies*

Prior to obtaining a marketing authorization in the European Union, applicants must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are provided in Regulation (EC) No 1901/2006, the so-called Paediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Paediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed, or an existing marketing authorization can be amended, the EMA determines that companies actually comply with the agreed studies and measures listed in each relevant PIP.

### *Regulatory data protection in the European Union*

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

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

### *Patent term extensions in the European Union and other jurisdictions*

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

### *Periods of authorization and renewals*

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

### *Regulatory requirements after marketing authorization*

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

### *Orphan drug designation and exclusivity*

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

in the European Union or, if such method exists, the drug will be of significant benefit to those affected by that condition.

An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance and the possibility to apply for a centralized European Union marketing authorization. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity. During this market exclusivity period, neither the EMA nor the European Commission or the member states can accept an application or grant a marketing authorization for a “similar medicinal product.” A “similar medicinal product” is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation because, for example, the product is sufficiently profitable not to justify market exclusivity.

### *Pediatric Exclusivity*

If an applicant obtains a marketing authorization in all European Union member states, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six-month period of qualifying patent protection through extension of the term of the SPC.

### *Brexit and the regulatory framework in the United Kingdom*

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020. Under the withdrawal agreement, there was a transitional period until December 31, 2020 (extendable by up to two years). On December 24, 2020, the United Kingdom and the European Union entered into a Trade and Cooperation Agreement. The agreement sets out certain procedures for approval and recognition of medical products in each jurisdiction. Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom, as the United Kingdom legislation now has the potential to diverge from European Union legislation. It remains to be seen how Brexit will impact regulatory requirements for product candidates and products in the United Kingdom in the long-term. The Medicines and Healthcare Regulatory Agency has recently published detailed guidance for industry and organizations to follow from January 1, 2021 now the transition period is over, which will be updated as the United Kingdom’s regulatory position on medicinal products evolves over time.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that “implements” and complements the European Union General Data Protection Regulation, or GDPR, has achieved Royal Assent on May 23, 2018 and is now effective in the United Kingdom, it is still unclear whether transfer of data from the European Economic Area, or EEA, to the United Kingdom will remain lawful under GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the United Kingdom will be treated like an European Union member state in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the United Kingdom will be a “third country” under the GDPR unless the European Commission adopts an adequacy decision in respect of transfers of personal data to the United Kingdom. The United Kingdom government has already determined that it considers all European Union 27 and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the European Union/EEA remain unaffected. We may, however, incur liabilities, expenses, costs and other operational losses under GDPR and applicable European

Union member states and the United Kingdom privacy laws in connection with any measures we take to comply with them.

#### *General Data Protection Regulation*

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

#### *Coverage, pricing and reimbursement*

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payers to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any product candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of such product candidates. Even if any product candidates we may develop are approved, sales of such product candidates will depend, in part, on the extent to which third-party payers, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for, such product candidates. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the product once coverage is approved. Third-party payers are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payers may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

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

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

If we obtain approval in the future to market in the United States any product candidates we may develop, we may be required to provide discounts or rebates under government healthcare programs or to certain government and private purchasers in order to obtain coverage under federal healthcare programs such as Medicaid. Participation in such programs may require us to track and report certain drug prices. We may be subject to fines and other penalties if we fail to report such prices accurately.

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

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

### *Healthcare Law and Regulation*

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other healthcare laws and regulations that may constrain business and/or financial arrangements.

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Restrictions under applicable federal and state healthcare laws and regulations, include the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid; the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to be made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government; the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make, improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment; and the federal transparency requirements known as the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members.

Further, some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

### *Healthcare reform*

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

In March 2010, the United States Congress enacted the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA, which, among other things, includes changes to the coverage and payment for drug products under government healthcare programs. Other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2030 under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or the Tax Act, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a



minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseparable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. On December 18, 2019, the Court of Appeals for the Fifth Circuit court affirmed the lower court's ruling that the individual mandate portion of the PPACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the PPACA. Thereafter, the U.S. Supreme Court agreed to hear this case. Oral argument in the case took place on November 10, 2020. On February 10, 2021, the Biden Administration withdrew the Department of Justice's support for this lawsuit. A ruling by the Court is expected sometime this year. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

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

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. To date, there have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. To those ends, President Trump issued five executive orders intended to lower the costs of prescription drug products, but it is unclear whether, and to what extent, these orders will remain in force under the Biden Administration. Further, on September 24, 2020, the Trump Administration finalized a rulemaking allowing states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants are required to demonstrate that their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. The FDA has issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

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

## **Human Capital Resources**

As of December 31, 2020, we had more than 100 full-time employees, including a total of 38 employees with M.D. or Ph.D. degrees. Of these full-time employees, approximately 75 employees are engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Our human capital resources objectives include identifying, recruiting, retaining, incentivizing and integrating our existing and newly hired employees. We design our compensation and benefit programs to help meet the needs of our employees, focusing on programs that promote well-being across all aspects of their lives, including healthcare, retirement planning and paid time off. We pay our employees competitively by performing a formal compensation benchmark analysis of our employees' salary, bonus potential, and equity awards twice per year and by linking annual bonuses to overall company performance. In addition to our compensation benchmarking analysis, we perform a gender pay gap analysis designed to ensure that women are paid equally to their male counterparts. Employees are paid based on our compensation philosophy, which includes paying employees competitively and at a rate consistent with an employee's position, knowledge and skills. Our equity incentive plans are designed to attract, retain and motivate our employees, consultants and directors through the granting of stock-based compensation awards.

We also strive to make our company an inclusive, safe and healthy workplace, with opportunities for each of our employees to grow and develop in their careers. Additionally, we promote opportunities for all employees to join our Acting for Justice and Women's Forums, which support and promote certain mutual objectives of both us and our employees, including inclusion and diversity.

## **Our Corporate Information**

We were incorporated under the laws of the state of Delaware on October 21, 2016 under the name Torus Therapeutics, Inc. On November 17, 2017 we changed our name to Generation Bio Co.

Our principal executive offices are located at 301 Binney Street, Cambridge, MA 02142 and our telephone number is (617) 655-7500. Our website address is <http://www.generationbio.com>. The information contained on, or accessible through, our website does not constitute part of this Annual Report. We have included our website address in this Annual Report solely as an inactive textual reference.

## **Available Information**

Our Internet address is [www.generationbio.com](http://www.generationbio.com). Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits, proxy and information statements and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act are available through the "Investors" portion of our website free of charge as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or SEC. Information on our website is not part of this Annual Report or any of our other securities filings unless specifically incorporated herein by reference. In addition, our filings with the SEC may be accessed through the SEC's Interactive Data Electronic Applications system at <http://www.sec.gov>. All statements made in any of our securities filings, including all forward-looking statements or information, are made as of the date of the document in which the statement is included, and we do not assume or undertake any obligation to update any of those statements or documents unless we are required to do so by law.

## ITEM 1A. RISK FACTORS

### Risk Factors

*Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report and in other documents that we file with the Securities and Exchange Commission, or SEC, in evaluating the Company and our business. Investing in our common stock involves a high degree of risk. If any of the following risks and uncertainties actually occur, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impact our business, prospects, financial condition and results of operations.*

### Risks related to our financial position and need for additional capital

*We have incurred significant losses since our inception, have no products approved for sale and we expect to incur losses over the next several years.*

Since inception, we have incurred significant operating losses. Our net losses were \$80.5 million and \$61.3 million for the years ended December 31, 2020 and 2019, respectively. As of December 31, 2020, we had an accumulated deficit of \$189.0 million. To date, we have funded our operations with the proceeds from instruments convertible into convertible preferred stock (which converted into convertible preferred stock in 2017), the sale of convertible preferred stock (which converted into common stock in 2020) and, most recently, from the sale of common stock in both our initial public offering, or IPO, and our follow-on public offering in January 2021. We have devoted substantially all of our financial resources and efforts to research and development. We are still in the early stages of development of our product candidates, and we have not commenced or completed clinical development. We expect to continue to incur significant expenses and operating losses over the next several years. Our operating expenses and net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

- continue our current research programs and conduct additional research programs;
- advance any product candidates we identify into preclinical and clinical development;
- expand the capabilities of our proprietary non-viral gene therapy platform;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- obtain, expand, maintain, defend and enforce our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel;
- ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- establish a commercial manufacturing source and secure supply chain capacity sufficient to provide commercial quantities of any product candidates we may develop for which we may obtain regulatory approval; and
- add operational, legal, compliance, financial and management information systems and personnel to support our research, product development, future commercialization efforts and operations as a public company.

Even if we obtain regulatory approval of and are successful in commercializing one or more of any product candidates we may develop, we will continue to incur substantial research and development and other expenditures to develop and market additional product candidates. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue.

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

We have not initiated clinical development of any product candidate and expect that it will be many years, if ever, before we have a product candidate ready for commercialization. To become and remain profitable, we must succeed in developing, obtaining the necessary regulatory approvals for and eventually commercializing a product or products that generate significant revenue. The ability to achieve this success will require us to be effective in a range of challenging activities, including:

- identifying product candidates and completing preclinical and clinical development of any product candidates we may identify;
- obtaining regulatory approval for any product candidates we may develop;
- manufacturing, marketing and selling any products for which we may obtain regulatory approval;
- achieving market acceptance of any product candidates we may develop for which we obtain regulatory approval as a viable treatment option; and
- satisfying any post-marketing requirements.

We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. We are currently only in the preclinical stage of our research programs. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

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

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we identify, continue the research and development of, initiate preclinical testing and clinical trials of and potentially seek marketing approval for any product candidates we may develop. In addition, if we obtain marketing approval for any product candidates we may develop, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales 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, on attractive terms or at all, we may be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

We believe that our existing cash, cash equivalents and marketable securities, including the net proceeds from the follow-on public offering that we completed in January 2021, will enable us to fund our operating expenses and capital expenditure requirements into 2024. However, we have based this estimate on assumptions that may prove to be wrong, and our operating plan may change as a result of many factors currently unknown to us. As a result, we could deplete our capital resources sooner than we currently expect and could be forced to seek additional funding sooner than planned.

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

- the identification of additional research programs and additional product candidates;
- the scope, progress, costs and results of preclinical and clinical development for any product candidates we may develop;

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- the costs, timing and outcome of regulatory review of any product candidates we may develop;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any product candidates we may develop for which we receive marketing approval;
- the costs and scope of the continued development of our non-viral gene therapy platform;
- the costs of satisfying any post-marketing requirements;
- the revenue, if any, received from commercial sales of product candidates we may develop for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting applications for patents, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims, including claims of infringement, misappropriation or other violations of third-party intellectual property;
- the costs of operational, financial and management information systems and associated personnel;
- the associated costs in connection with any acquisition of in-licensed products, intellectual property and technologies; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, even if we successfully identify and develop product candidates and those are approved, we may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all, and such revenues may not be sufficient to sustain our operations. 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.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize any product candidates. We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and, if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. We could be required to seek collaborators for product candidates we may develop at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to product candidates we may develop in markets where we otherwise would seek to pursue development or commercialization ourselves.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidate we may develop, or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations. Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

### ***Raising additional capital may cause dilution to our stockholders, restrict our operations, or require us to relinquish rights to our technologies or product candidates.***

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and/or licensing arrangements. We do not have any committed external source of funds. To the extent that we raise additional

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capital through the sale of equity or convertible debt securities, our stockholders' ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures, declaring dividends or encumbering our assets to secure future indebtedness.

If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed or on terms acceptable to us, we would be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

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

We commenced operations in 2016, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital, conducting research activities and filing and prosecuting patent applications. All of our research programs are still in the research or preclinical stage of development, and their risk of failure is high. We have not yet demonstrated our ability to initiate or complete any clinical trials, obtain marketing approvals, manufacture a commercial scale product or arrange for a third party to do so on our behalf, or conduct sales, marketing and distribution activities necessary for successful product commercialization. Consequently, any predictions our stockholders make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing genetic medicine products.

Our limited operating history, particularly in light of the rapidly evolving genetic medicine field, may make it difficult to evaluate our technology and industry and predict our future performance. Our limited history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early stage companies in rapidly evolving fields. If we do not address these risks successfully, our business will suffer.

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

### ***Our ability to utilize our net operating loss carryforwards may be subject to limitations.***

We have a history of cumulative losses and anticipate that we will continue to incur significant losses in the foreseeable future; thus, we do not know whether or when we will generate taxable income necessary to utilize our net operating losses, or NOLs, or research and development tax credit carryforwards. As of December 31, 2020, we had federal NOLs of \$177.3 million and state NOLs of \$174.7 million.

In general, under Sections 382 and 383 of the U.S. Internal Revenue Code of 1986, as amended, or the Code, and corresponding provisions of state law, a corporation that undergoes an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three-year period, is subject to limitations on its ability to utilize its pre-change NOLs and research and development tax credit carryforwards to offset future taxable income. We have not conducted a study to assess whether any such ownership changes have occurred. We may have experienced such ownership changes in the past and may experience such ownership changes in the future as a result of changes in our stock ownership (which may be outside our control). As a result, if, and to the extent that, we earn net taxable income, our ability to use our

pre-change NOLs and research and development tax credit carryforwards to offset such taxable income may be subject to limitations.

There is also a risk that due to regulatory changes, such as suspensions on the use of NOLs, or other unforeseen reasons, our existing NOLs could expire or otherwise become unavailable to offset future income tax liabilities. As described below in “Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition,” the Tax Act, as amended by the CARES Act includes changes to U.S. federal tax rates and the rules governing NOL carryforwards that may significantly impact our ability to utilize our NOLs to offset taxable income in the future. In addition, state NOLs generated in one state cannot be used to offset income generated in another state. For these reasons, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes.

### **Risks related to discovery and development**

***We are very early in our development efforts. We have not identified any product candidates for Investigational New Drug, or IND, -enabling studies or clinical development and as a result it will be years before we commercialize a product candidate, if ever. If we are unable to identify and advance product candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them, or experience significant delays in doing so, our business will be materially harmed.***

We are very early in our development efforts and have invested our research efforts to date in developing our platform. We have a portfolio of programs, including those listed in “Business—Our portfolio,” that are in early stages of preclinical development and have not identified any product candidates for IND-enabling studies or clinical development. We may never identify any product candidates or advance to clinical-stage development. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. We currently generate no revenue from sales of any product, and we may never be able to develop or commercialize a marketable product.

Commencing clinical trials in the United States is subject to acceptance by the U.S. Food and Drug Administration, or FDA, of an IND application and finalizing the trial design based on discussions with the FDA and other regulatory authorities. In the event that the FDA requires us to complete additional preclinical studies or we are required to satisfy other FDA requests prior to commencing clinical trials, the start of our first clinical trials may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence any clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials or impose stricter approval conditions than we currently expect. There are equivalent processes and risks applicable to clinical trial applications in other countries, including countries in the European Union.

Commercialization of any product candidates we may develop will require preclinical and clinical development; regulatory and marketing approval in multiple jurisdictions, including by the FDA and the European Medicines Agency, or EMA; obtaining manufacturing supply, capacity and expertise; building of a commercial organization; and significant marketing efforts. The success of product candidates we may identify and develop will depend on many factors, including the following:

- timely and successful completion of preclinical studies, including toxicology studies, biodistribution studies and minimally efficacious dose studies in animals, where applicable;
- effective INDs or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for any product candidates we may develop;
- successful enrollment and completion of clinical trials, including under the FDA’s current Good Clinical Practices, or GCPs, current Good Laboratory Practices, or cGLPs, and any additional regulatory requirements from foreign regulatory authorities;

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- positive results from our future clinical programs that support a finding of safety and effectiveness and an acceptable risk-benefit profile in the intended populations of any product candidates we may develop;
- receipt of marketing approvals from applicable regulatory authorities;
- establishment of arrangements through our own facilities or with third-party manufacturers for clinical supply and, where applicable, commercial manufacturing capabilities;
- establishment, maintenance, defense and enforcement of patent, trademark, trade secret and other intellectual property protection or regulatory exclusivity for any product candidates we may develop;
- commercial launch of any product candidates we may develop, if approved, whether alone or in collaboration with others;
- acceptance of the benefits and use of any product candidates we may develop, including method of administration, if and when approved, by patients, the medical community and third-party payers;
- effective competition with other therapies;
- maintenance of a continued acceptable safety, tolerability and efficacy profile of any product candidates we may develop following approval; and
- establishment and maintenance of healthcare coverage and adequate reimbursement by payers.

If we do not succeed in one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize any product candidates we may develop, which would materially harm our business. If we are unable to advance our product candidates to clinical development, obtain regulatory approval and ultimately commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

***We may encounter substantial delays in commencement, enrollment or completion of our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, which could prevent us from commercializing any product candidates we determine to develop on a timely basis, if at all.***

The risk of failure for any product candidates we determine to develop is high. It is impossible to predict when or if any product candidate would prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of product candidates in humans. We have not yet begun or completed a clinical trial of any product candidate. Clinical trials may fail to demonstrate that our product candidates are safe for humans and effective for indicated uses. Even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application.

Before we can commence clinical trials for a product candidate, we must complete extensive preclinical testing and studies that support our IND applications and other regulatory filings. We cannot be certain of the timely completion or outcome of our preclinical testing and studies and cannot predict if the FDA will accept our proposed clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of any product candidates. As a result, we cannot be sure that we will be able to submit IND applications for our preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of IND applications will result in the FDA allowing clinical trials to begin. Furthermore, product candidates are subject to continued preclinical safety studies, which may be conducted concurrently with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

Further, timely completion of preclinical activities is dependent upon the availability of preclinical sites, researchers, investigators and research materials, which may be adversely affected by global health matters, such



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as pandemics. We and our contract development and manufacturing organizations and contract research organizations experienced a temporary reduction in the capacity to undertake research scale production and to execute some preclinical studies, and we may face disruptions in the future that affect our ability to initiate and complete preclinical studies and to procure items that are essential for our research and development activities.

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

Identifying and qualifying patients to participate in clinical trials of any product candidates we may develop is critical to our success. 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. Patient enrollment and trial completion is affected by factors including:

- perceived risks and benefits of novel genetic medicine-based approaches;
- size of the patient population, in particular for rare diseases, and process for identifying patients;
- design of the trial protocol;
- eligibility and exclusion criteria;
- perceived risks and benefits of the product candidate under study;
- availability of competing therapies and clinical trials;
- severity of the disease or disorder under investigation;
- proximity and availability of clinical trial sites for prospective patients;
- ability to obtain and maintain patient consent;
- risk that enrolled patients will drop out before completion of the trial;
- travel restrictions as a result of the ongoing COVID-19 pandemic;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

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

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

- delays in reaching a consensus with regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations, or CLROs, and clinical trial sites;
- delays in opening clinical trial sites or obtaining required institutional review board, or IRB, or independent ethics committee approval, or the equivalent review groups for sites outside the United States, at each clinical trial site;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or after an inspection of our clinical trial operations or trial sites;
- failure by us, any CLROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's GCPs;
- failure by physicians to adhere to delivery protocols leading to variable results;

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- delays in the testing, validation, manufacturing and delivery of any product candidates we may develop to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a trial;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- impact of the COVID-19 pandemic, our response thereto and responses by other businesses and governments;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- occurrence of serious adverse events associated with a product candidate in development by another company, which are viewed to outweigh its potential benefits, and which may negatively impact the perception of our product due to a similarity in technology or approach;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the legal or regulatory regimes domestically or internationally related to patient rights and privacy; or
- lack of adequate funding to continue the clinical trial.

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

Additionally, if the results of future clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with any product candidates we may develop, we may:

- be delayed in obtaining marketing approval for 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 that includes significant use or distribution restrictions or safety warnings;
- be subject to changes in the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw, or suspend, their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

***Genetic medicine is an emerging area of drug development that poses many scientific and other risks. We have only limited prior experience in genetic medicine research and manufacturing and no prior experience in genetic medicine clinical development. Our lack of experience for our genetic medicine programs may limit our ability to be successful or may delay our development efforts.***

Genetic medicine is an emerging field of drug development with only a small number of genetic medicines having received FDA or EMA approval to date. Our genetic medicine research programs are still at an early

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

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

We will need to build our internal and external capabilities in designing and executing a genetic medicine clinical trial. There are many known and unknown risks involved in translating preclinical development of gene therapies to clinical development, including selecting appropriate endpoints and dosage levels for dosing humans based on preclinical data. Furthermore, our genetic medicine programs are initially targeting rare diseases with relatively small populations, which limits the pool of potential subjects for our genetic medicine clinical trials. If we are unable to initiate and conduct our genetic medicine clinical trials in a manner that satisfies our expectations or regulatory requirements, the value of our genetic medicine programs may be diminished.

***Our non-viral gene therapy platform is based on novel technologies that are unproven, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all.***

We have concentrated our research and development efforts on our non-viral gene therapy platform, and our future success depends on the successful development of our platform.

However, the technologies that comprise our platform are new and largely unproven. These technologies have not been clinically tested and the scientific evidence to support the feasibility of developing product candidates based on those technologies is both preliminary and limited. Successful development of product candidates by us will require solving a number of issues, including the expansion of our cell-targeted lipid nanoparticle delivery system, or ctLNP, delivery system to tissues beyond the liver and retina and obtaining expression levels sufficient to address or ameliorate each target disease or indication. There can be no assurance we will be successful in solving any or all of these issues. We have concentrated our research efforts to date on developing the components of our platform, and our future success is highly dependent on the successful development of our closed-ended DNA, or ceDNA, constructs, our ctLNP delivery system and therapeutic applications of these technologies. We may decide to alter or abandon our initial programs as new data become available and we gain experience in developing our therapeutics. We cannot be sure that our technologies will yield satisfactory products that are safe and effective, scalable or profitable in any indication we pursue.

There can be no assurance that any development problems we experience in the future related to our non-viral gene therapy platform will not cause significant delays or unanticipated costs, or that such development problems can be solved. We may also experience delays in developing a sustainable, reproducible and scalable manufacturing process or transferring that process to commercial partners, which may prevent us from initiating or conducting clinical trials or commercializing our products on a timely or profitable basis, if at all.

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In addition, the clinical trial requirements of the FDA, the EMA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate may vary according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates can be more expensive and take longer than for other, better known or extensively studied pharmaceutical or other product candidates, and even more so for product candidates intended to treat diseases for which there are approved therapies that may allow a normal life span as compared with those intended to treat serious and life-threatening diseases for which there are no other treatment options available. There are approved therapies for our lead indications, hemophilia A and PKU, in some jurisdictions in the world. As a result, the regulatory burden to initiate clinical trials or to obtain regulatory approval of any product candidate we may develop for those indications may be more extensive in those jurisdictions than for product candidates intended to treat diseases that are life threatening and for which no therapies are approved. Only a small number of non-viral gene therapies have successfully reached the clinical trial phase of development, limiting insight into the regulatory review process for this field of genetic medicine. Requirements by regulatory authorities for any product candidate we may develop may change in response to the availability of other therapies for the indication our product candidates are designed to treat or to issues observed in clinical trials of genetic medicines of other companies, even if using technology that differs from ours. We intend to pursue genetic medicine programs in both rare and prevalent diseases, some of which may have available approved therapies. As a result, it is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals in either the United States or the European Union for any product candidates we may develop or how long it will take to commercialize any product candidate that receives marketing approval.

***If any product candidates we may develop cause undesirable side effects or have other unexpected adverse properties, such side effects or properties could delay or prevent regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.***

We have not evaluated any product candidates in human clinical trials. Moreover, there have been only a limited number of clinical trials involving the use of non-viral gene therapies and none involving ceDNA constructs or other technology similar to our technology. It is impossible to predict when or if any product candidates we may develop will prove safe in humans. In the genetic medicine field, there have been several significant adverse events from gene therapy treatments in the past, including reported cases of leukemia and death. There can be no assurance that our technologies will not cause undesirable side effects.

We use a ctLNP delivery system to deliver our ceDNA constructs. Lipid nanoparticles have been shown to induce necrosis in the liver at certain doses and induce infusion related reactions, as well as to initiate systemic inflammatory responses. While our ctLNPs are a new generation of LNP, there can be no assurance that our ctLNPs will not have undesired effects. Our ctLNPs could contribute, in whole or in part, to immune reactions, infusion reactions, complement reactions or antibody reactions. In addition, certain aspects of our non-viral gene therapies may induce immune reactions from the lipid as well as adverse reactions within liver pathways or degradation of the LNP into its component molecules or metabolites, any of which could lead to significant adverse events in one or more of our future clinical trials. Many of these types of side effects have been seen for LNPs. Once delivered to target cells, DNA-based payloads, such as those carried by our ceDNA constructs, may interact with host proteins or chromosomal DNA in the cell endosome, cytosol or nucleus.

Adeno-associated virus, or AAV, genomes have been shown in some cases to initiate intracellular immune activation, which can lead to transcriptional changes, and local tissue interferon responses, which may lead to immune infiltrates and tissue damage. AAV genetic material may also integrate into the host chromosome, which could contribute to modified cell function transformation. There may be uncertainty as to the underlying cause of any such adverse event, which would make it difficult to accurately predict side effects in future clinical trials and would result in significant delays in our programs.

If any product candidates we develop are associated with serious adverse events, undesirable side effects or unexpected characteristics, we may need to abandon their development or limit development to certain uses or subpopulations in which the serious adverse events, undesirable side effects or other characteristics are less

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prevalent, less severe or more acceptable from a risk-benefit perspective, any of which would have a material adverse effect on our business, financial condition, results of operations and prospects. Many product candidates that initially showed promise in early stage testing for treating cancer or other diseases have later been found to cause side effects that prevented further clinical development of the product candidates.

If in the future we are unable to demonstrate that such side effects were caused by factors others than our product candidates, the FDA, the EMA or other regulatory authorities could order us to cease further development of, or deny approval of, any product candidates for any or all targeted indications. Even if we are able to demonstrate that any future serious adverse events are not product-related, and regulatory authorities do not order us to cease further development of our product candidates, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any product candidate, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects significantly.

Regulatory approval of and/or demand for our potential products will depend in part on public acceptance of the use of genetic medicine for the prevention or treatment of human diseases. Safety issues that might arise in trials for gene therapies other than our own could adversely impact public attitudes towards our platform and product candidates notwithstanding that the gene therapies we are developing are non-viral.

There are a number of clinical trials of gene therapies ongoing. There is a potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry genetic material. Possible adverse side effects that may occur with treatment with gene therapy products include an immunologic reaction early after administration that could substantially limit the effectiveness of the treatment or represent safety risks for patients.

Any of these events could prevent us from achieving or maintaining market acceptance of any product candidates we may develop and could significantly harm our business, prospects, financial condition and results of operations.

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

We are in the early stage of research in the development of our platform and have not identified any product candidates or conducted any IND-enabling studies or any clinical trials. As a result, our belief in the capabilities of our platform is based on early research and preclinical studies. However, the results of preclinical studies may not be predictive of the results of preclinical studies or clinical trials, and the results of any early-stage clinical trials may not be predictive of the results of later clinical trials. In addition, initial success in clinical trials may not be indicative of results obtained when such trials are completed. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. Our future clinical trials may not ultimately be successful or support further clinical development of any product candidates we may develop. There is a high failure rate for product candidates proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving encouraging results in earlier studies. Any such setbacks in our clinical development could materially harm our business and results of operations.

### ***We may not be successful in our efforts to identify, discover or develop potential product candidates.***

The success of our business depends primarily upon our ability to identify, develop and commercialize product candidates based on our non-viral gene therapy platform. All of our product development programs are still in the research or preclinical stage of development. Our research programs may fail to identify potential product

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candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates, our potential product candidates may be shown to have harmful side effects in preclinical *in vitro* experiments or animal model studies, they may not show promising signals of therapeutic effect in such experiments or studies or they may have other characteristics that may make the product candidates impractical to manufacture, unmarketable or unlikely to receive marketing approval.

In addition, although we believe our platform will position us to rapidly expand our portfolio of programs beyond our current programs, we have not yet successfully developed any product candidate and our ability to expand our portfolio may never materialize. The process by which we identify and disclose product candidates may fail to yield product candidates for clinical development for a number of reasons, including those discussed in these risk factors and also:

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

If we are unable to identify and discover suitable product candidates for clinical development, this would adversely impact our business strategy and our financial position and share price and could potentially cause us to cease operations.

***The genetic medicine field is relatively new and evolving rapidly. We are focusing our research and development efforts on our non-viral gene therapy platform, but other gene therapy technologies may be discovered that provide significant advantages over our platform, which could materially harm our business.***

To date, we have focused our efforts on the advancement of our non-viral gene therapy platform, which is designed to overcome the limitations of current viral gene therapy approaches. However, while these modalities have demonstrated their limitations, there are many companies that are developing new genetic medicines, including viral gene therapies, gene editing, base editing of either DNA or RNA and messenger RNA, or mRNA, -based therapeutics. There can be no certainty that these companies will not develop genetic medicines that address some of these limitations and will be considered to have advantages over our non-viral gene therapy platform. For example, in December 2019, Dyno Therapeutics announced a new technique for AAV delivery that allows the researchers to engineer the virus shell to deliver the gene package to the exact cell type in the body they intend to treat. This new method may reduce concerns about off-target AAV delivery and make it a more attractive delivery system. Additionally, Selecta Biosciences and AskBio are developing a transient immunosuppressive approach with AAV and a new formulation of rapamycin that is designed to shield AAV from an immune response, potentially enabling redosing to improve efficacy, initiate treatment in children or extend the time of effective therapy.

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

Because we have limited financial and managerial resources, we focus on research programs and expect to focus on product candidates that we identify for specific indications among many potential options. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential, or we may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable medicines. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

We will need to increase our insurance coverage if we commence clinical trials or if we commence commercialization of any product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. If a successful clinical trial or product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

#### **Risks relating to manufacturing**

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

Genetic medicine drug products are complex and difficult to manufacture. We have an established cGMP-ready process at the 200-liter scale which we have successfully transferred to external contract development and

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manufacturing organizations, or CDMOs, to supply our gene therapies for IND-enabling preclinical studies and early clinical trials. We believe that we will be able to enter into arrangements with existing and/or additional CDMOs to provide commercial supply. We may also seek to eventually establish our own manufacturing facility for long-term commercial supply.

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

Given the nature of biologics manufacturing, there is a risk of contamination during manufacturing. Any contamination could materially harm our ability to produce product candidates on schedule and could harm our results of operations and cause reputational damage. Some of the raw materials that we anticipate will be required in our manufacturing process, such as Sf9 cells, are derived from biologic sources. Such raw materials may be difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of any product candidates we may develop could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could materially harm our development timelines and our business, financial condition, results of operations and prospects.

***Our non-viral gene therapy platform is novel, and the combination of novel constructs with untested scaling may cause us to experience delays in satisfying regulatory authorities or production problems that result in delays in our development or commercialization programs, limit the supply of any product candidates we may develop or otherwise harm our business.***

Our non-viral gene therapy platform is novel and the manufacture of products on the basis of our platform is untested at a large scale. Problems with the manufacturing process, even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims, insufficient inventory or potentially delay progression of our preclinical or clinical development of any product candidates we may develop. If we successfully develop product candidates, we may encounter problems achieving adequate quantities and quality that meet FDA, EMA or other comparable applicable foreign standards or specifications with consistent and acceptable production yields and costs. The ability to scale our manufacturing and maintain the manufacturing process at the same levels of quality and efficacy that we are currently manufacturing is yet to be tested. If we or our CDMOs are unable to scale our manufacturing at the same levels of quality and efficiency, we may not be able to supply the required number of doses for clinical trials or commercial supply, and our business could be harmed.

***Manufacturing the ctLNP component of a potential product candidate may be complex and difficult, and we could experience delays in satisfying regulatory authorities or production problems that result in delays in our development or commercialization, limit the supply of any product candidates we may develop or otherwise harm our business.***

Many product candidates we may develop will require the manufacture of the ctLNP component, which may require processing steps that are more complex than those required for current products that utilize LNPs. In order to manufacture ctLNPs that are specialized for a given platform program, we may need to add biologic ligands to existing LNPs. This process is challenging and may pose a risk to our ability to manufacture on a scale sufficient to meet clinical and commercial needs.



***Testing of and changes to methods of product candidate manufacturing or formulation may result in additional costs or delay.***

As product candidates proceed through preclinical studies to clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are tested and then altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives.

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

We may make changes to our manufacturing methods as part of our product development activities. Any such changes could cause any product candidates we may develop to perform differently and affect the results of clinical trials conducted with the materials manufactured using altered processes. Such changes may also require additional testing, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue.

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

***We currently depend on a small number of third-party suppliers for our drug substance and drug product, and we expect to continue to depend on third-party suppliers for materials used in the manufacture of any product candidates we may develop, and the loss of these third-party suppliers or their inability to supply us with adequate materials, particularly those raw materials that are in short supply, could harm our business.***

We currently rely on a small number of third-party suppliers for our drug substance and drug product and expect to continue to rely on third-party suppliers for certain materials and components required for the production of any product candidates we may develop. Our dependence on these third-party suppliers and the challenges we may face in obtaining and maintaining adequate supplies of materials involve several risks, including limited control over pricing, availability and quality and delivery schedules. There is substantial demand and limited supply for certain of the raw materials used to manufacture genetic medicine products and these raw materials are usually sole-sourced, as there are a limited number of qualified suppliers. This limited supply, combined with any problems that may arise during the manufacturing process development, may create long lead times to manufacture or procure starting materials. The progress of our non-viral gene therapy platform is highly dependent on these suppliers providing us or our contract manufacturer with the necessary starting materials that meet our requirements in a timely manner. As a small company, our negotiation leverage is limited, and we are likely to get lower priority than our competitors that are larger than we are. We cannot be certain that our suppliers will continue to provide us with the quantities of these raw materials that we require or satisfy our anticipated specifications and quality requirements.

Any supply interruption in limited or sole-sourced raw materials could materially harm our ability to manufacture any product candidates we may develop until a new source of supply, if any, could be identified and qualified. We may be unable to find a sufficient alternative supply channel in a reasonable time or on commercially reasonable terms. Any performance failure on the part of our suppliers could delay the development and potential commercialization of any product candidates we may develop, including limiting supplies necessary for clinical trials and regulatory approvals, which would have a material adverse effect on our business.

#### **Risks related to our dependence on third parties**

***We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, 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 product manufacturing, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to many of these items, including CDMOs for the manufacturing of any product candidates we test in preclinical or clinical development, as well as contract research organizations, or CROs for the conduct of our animal testing and research. Any of these third parties may terminate their engagements with us 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 IND-enabling studies and clinical trials are conducted in accordance with the study plan and protocols.

Although we intend to design the clinical trials for any product candidates we may develop, CLROs will conduct some or all of the clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct future preclinical studies and clinical trials will also result in less direct control over the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our preclinical studies and clinical trials and may subject us to unexpected cost increases that are beyond our control. If the CLROs and other third parties do not perform preclinical studies and future clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development, regulatory approval and commercialization of any product candidates we may develop may be delayed, we may not be able to obtain regulatory approval and commercialize our product candidates or our development programs may be materially and irreversibly harmed. If we are unable to rely on preclinical and clinical data collected by our CLROs and other third parties, we could be required to repeat, extend the duration of or increase the size of any preclinical studies or clinical trials we conduct and this could significantly delay commercialization and require greater expenditures.

The COVID-19 pandemic has impacted, and may continue to impact, our third-party CDMOs, CROs and CLROs, including through the effects of facility closures, reductions in operating hours, staggered shifts and other social distancing efforts, labor shortages, decreased productivity and unavailability of materials or

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components. While we maintain an inventory of materials necessary to conduct our research and any preclinical studies, a prolonged outbreak could lead to shortages in these materials.

If third parties 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 studies and clinical trials required to support future IND submissions and approval of any product candidates we may develop.

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

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

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

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 or at all if they are affiliated with our competitors;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities, particularly if they are under contract with our competitors;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and

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- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier.

Any of these events could lead to clinical trial delays 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.

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

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

***We may from time to time be dependent on single-source suppliers for some of the components and materials used in, and the processes required to develop, our development candidates and investigational medicines.***

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

If we have to switch to a replacement supplier, the manufacture and delivery of our development candidates or investigational medicines could be interrupted for an extended period, which could adversely affect our business. Establishing additional or replacement suppliers for any of the components or processes used in our investigational medicines, if required, may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. While we seek to maintain adequate inventory of the single source components and materials used in our products, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand for our investigational medicines.

***If we or any contract manufacturers and suppliers we engage 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 and any contract manufacturers and suppliers we engage are subject to numerous federal, state and local environmental, health, and safety laws, regulations and permitting requirements, including those governing laboratory procedures; the generation, handling, use, storage, treatment and disposal of hazardous and regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air and water; and

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employee health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste. 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. Under certain environmental laws, we could be held responsible for costs relating to any contamination at third-party facilities. We also could incur significant costs associated with civil or criminal fines and penalties.

Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our research and product development efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. 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, this insurance may not provide adequate coverage against potential liabilities. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws, regulations and permitting requirements. These current or future laws, regulations and permitting requirements may impair our research, development or production efforts. Failure to comply with these laws, regulations and permitting requirements also may result in substantial fines, penalties or other sanctions or business disruption, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Any third-party contract manufacturers and suppliers we engage will also be subject to these and other environmental, health and safety laws and regulations. Liabilities they incur pursuant to these laws and regulations could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

***We expect to rely on third parties to conduct, supervise and monitor IND-enabling studies and clinical studies, and if these third parties perform in an unsatisfactory manner, it may harm our business.***

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

We and our CROs and CLROs will be required to comply with the FDA's GCPs for conducting, recording and reporting the results of IND-enabling studies and clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces these GCPs through periodic inspections of study sponsors, principal investigators and clinical trial sites. If we or our CROs or CLROs fail to comply with applicable GCPs, the preclinical and clinical data generated in our studies may be deemed unreliable and the FDA may require us to perform additional studies before approving any marketing applications. Upon inspection, the FDA may determine that our studies did not comply with GCPs.

Our CLROs and CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CLROs and CROs may

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also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our CROs or CLROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols or regulatory requirements, or for any other reasons, our studies may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize any product candidates we may develop. As a result, our financial results and commercial prospects would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

***We may enter into collaborations with third parties for the research, development and commercialization of certain of the product candidates we may develop. If any such collaborations are not successful, we may not be able to capitalize on the market potential of those product candidates.***

We may seek third-party collaborators for the research, development and commercialization of certain of the product candidates we may develop. If we enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of any product candidates we may seek to develop with them. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. We cannot predict the success of any collaboration that we enter into.

Collaborations involving our research programs or any product candidates we may develop pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of any product candidates we may develop or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay programs, preclinical studies or clinical trials, provide insufficient funding for programs, preclinical studies or clinical trials, stop a preclinical study or clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with any product candidates we may develop if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators may be acquired by a third party having competitive products or different priorities;
- collaborators with marketing and distribution rights to one or more medicines may not commit sufficient resources to the marketing and distribution of such medicine or medicines;
- collaborators may not properly obtain, maintain, enforce or defend our intellectual property or proprietary rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development, or commercialization of our medicines or any product candidates we may develop or that result in costly litigation or arbitration that diverts management attention and resources;
- we may lose certain valuable rights under certain circumstances, including if we undergo a change of control;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates we may develop; and

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- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated.

If our collaborations do not result in the successful development and commercialization of product candidates, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed, and we may need additional resources to develop product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to find a suitable replacement collaborator or attract new collaborators, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report apply to the activities of our collaborators.

These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators, and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of several factors. If we license rights to any product candidates we or our collaborators may develop, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

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

If conflicts arise between our corporate or academic collaborators or strategic partners and us, the other party may act in a manner adverse to us and could limit our ability to implement our strategies. Some of our academic collaborators are conducting multiple product development efforts within each area that is the subject of the collaboration with us. Our collaborators or strategic partners, however, may develop, either alone or with others, products in related fields that are competitive with the product candidates we may develop that are the subject of these collaborations with us. Competing products, either developed by the collaborators or strategic partners or to which the collaborators or strategic partners have rights, may result in the withdrawal of partner support for our product candidates we may develop.

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

***If we are not able to establish collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans.***

Our product development and research programs and the potential commercialization of any product candidates we may develop will require substantial additional cash to fund expenses. For some of the product candidates we may develop, we may decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and

expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, the EMA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization, reduce the scope of any sales or marketing activities, or increase our own expenditures on the development of the product candidate.

### **Risks related to commercialization**

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

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

There are numerous companies that are selling or developing genetic medicines, including in indications for which we may develop our non-viral gene therapies. These companies include viral gene therapy companies such as BioMarin Pharmaceuticals, Inc., Homology Medicines, Inc., Adverum Biotechnologies, Inc., Ultragenyx Pharmaceutical Inc. and Hoffmann La Roche Ltd; gene editing companies such as Crispr Therapeutics AG, Intellia Therapeutics, Inc. and Editas Medicine, Inc.; and mRNA companies such as Moderna, Inc. See "Business—Competition" for additional information regarding competition.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than our product candidates or that would render any product candidates that we may develop obsolete or non-competitive. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do.



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Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

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

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

- the efficacy and safety of such product candidates as demonstrated in clinical trials;
- the potential advantages and limitations compared to alternative treatments;
- the effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments;
- the clinical indications for which the product is approved;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products, if approved, together with other medications.

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

The initial target platforms in our pipeline are indications with small patient populations. For product candidates that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such product candidates must be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product candidate that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement

for any future product candidates from third-party payers, the adoption of those product candidates and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved.

We expect that coverage and reimbursement by third-party payers will be essential for most patients to be able to afford these treatments. Accordingly, sales of our future product candidates will depend substantially, both domestically and internationally, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payers. 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 by government authorities for new products are typically made by the Centers for Medicare & Medicaid Services, or CMS, since CMS decides whether and to what extent a new product will be covered and reimbursed under Medicare. Private payers tend to follow CMS to a substantial degree. However, one payer's determination to provide coverage for a product does not assure that other payers will also provide coverage for the drug product. Further, a payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Reimbursement agencies in the European Union may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European countries.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as any product candidates we may develop. In many countries, particularly the countries of the European Union, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay or might even prevent our commercial launch of the product, possibly for lengthy periods of time. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In general, the prices of products under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for product candidates. Accordingly, in markets outside the United States, the reimbursement for any product candidates we may develop may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Moreover, increasing efforts by governmental and third-party payers, in the United States and internationally, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for any product candidates we may develop. We expect to experience pricing pressures in connection with the sale of any product candidates we may develop due to the trend toward managed healthcare, the increasing influence of certain third-party payers, such as health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market. Recently there have been instances in which third-party payers have refused to reimburse treatments for patients for whom the treatment is indicated in the FDA-approved product label. Even if we are successful in obtaining FDA approvals to commercialize our product candidates, we cannot guarantee that we will be able to secure reimbursement for all patients for whom treatment with our product candidates is indicated.

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In addition to CMS and private payers, professional organizations such as the American Medical Association, or the AMA, can influence decisions about reimbursement for new products by determining standards for care. In addition, many private payers contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our product candidates. Even if favorable coverage and reimbursement status is attained for one or more product candidates for which we or our collaborators receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product for which we have obtained marketing approval, we will need to establish a sales, marketing and distribution organization, either ourselves or through collaborations or other arrangements with third parties.

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

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

- our inability to recruit, train and retain adequate numbers of effective sales, marketing, coverage or reimbursement, customer service, medical affairs and other support personnel;
- the inability of sales personnel to educate adequate numbers of physicians on the benefits of any future products;
- the inability of reimbursement professionals to negotiate arrangements for formulary access, reimbursement and other acceptance by payers;
- the inability to price our products at a sufficient price point to ensure an adequate and attractive level of profitability;
- restricted or closed distribution channels that make it difficult to distribute our products to segments of the patient population;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and we enter into arrangements with third parties to perform these services, our product revenues and our profitability, if any, are likely to be lower than if we were to market, sell and distribute any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute any product candidates we may develop or may be unable to do so on terms that are acceptable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing any product candidates we may develop.

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

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Amendment, or the PPACA, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have an adverse effect on the future commercial prospects for our biological products.

There is a risk that any product candidates we may develop that are approved as a biological product under a BLA would not qualify for the 12-year period of exclusivity or that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider any product candidates we may develop to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for nonbiological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

***If the market opportunities for any product candidates we may develop are smaller than we believe they are, our potential revenues may be adversely affected, and our business may suffer. Because the target patient populations for many of the initial product candidates we may develop are small, we must be able to successfully identify patients and achieve a significant market share to maintain profitability and growth.***

We are focusing our initial research and product development on treatments for rare genetically defined diseases; as a result, the relevant patient population may be small. Our projections 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 product candidates we may develop, are based on estimates. These estimates may prove to be incorrect and new studies may change the estimated incidence or prevalence of these diseases. The number of patients in the United States, Europe and elsewhere may turn out to be lower than expected, and patients may not be amenable to treatment with our product candidates we may develop, or may become increasingly difficult to identify or gain access to, all of which would adversely affect our business, financial condition, results of operations and prospects. Additionally, because of the potential that any product candidates we may develop could cure a target disease, we may not receive recurring revenues from patients and may deplete the patient population prevalence through curative therapy.

**Risks related to our intellectual property**

***Although we own and license a number of pending patent applications which have not yet issued as patents, we do not currently own or exclusively in-license any issued patents relating to any product candidates we may develop or technology, including with respect to our ceDNA constructs, ctLNP delivery system and manufacturing process. If we or our licensors are unable to obtain, maintain and defend patent and other intellectual property protection for our product candidates and technology, or if the scope of the patent or***

***other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully develop and commercialize any product candidates we may develop or our technology may be adversely affected due to such competition.***

Our success depends in large part on our and our licensors' ability to obtain and maintain patent and other intellectual property protection in the United States and other jurisdictions with respect to any product candidates we may develop and our technology, including our ceDNA constructs, ctLNP delivery system, manufacturing processes and their respective components, formulations, combination therapies, methods of treatment, processes and development that are important to our business, as well as successfully defending these patents and other intellectual property against third-party challenges. We and our licensors have sought, and will seek, to protect our proprietary position by filing patent applications in the United States and abroad related to certain technologies and our platform that are important to our business. However, our patent portfolio is at an early stage and we currently do not own or exclusively license any issued patents in any jurisdiction. Moreover, there can be no assurance as to whether or when our patent applications will issue as granted patents. Our ability to stop third parties from making, using, selling, marketing, offering to sell, importing and commercializing any product candidates we may develop and our technology is dependent upon the extent to which we have rights under valid and enforceable patents and other intellectual property that cover our platform and technology. If we are unable to secure, maintain, defend and enforce patents and other intellectual property with respect to any product candidates we may develop and technology, it would have a material adverse effect on our business, financial condition, results of operations and prospects.

We own certain patent applications, and exclusively in-license from University of Massachusetts as represented by and solely on behalf of its Medical School, or UMass, and Voyager Therapeutics, Inc. certain other patent applications, which cover our ceDNA platform structure, use and/or function, our ctLNP platform and its use, and ceDNA manufacturing processes, as applicable. Our pending Patent Cooperation Treaty, or PCT, patent applications are not eligible to become issued patents until, among other things, we file a national stage patent application within 30 to 32 months, depending on the jurisdiction, from such application's priority date in the jurisdictions in which we are seeking patent protection. Similarly, our pending provisional patent applications are not eligible to become issued patents until, among other things, we file a non-provisional patent application within 12 months of such provisional patent application's filing date. If we do not timely file such national stage patent applications or non-provisional patent applications, we may lose our priority date with respect to such PCT or provisional patent applications, respectively, and any patent protection on the inventions disclosed in such PCT or provisional patent applications, respectively. While we and our licensors intend to timely file national stage and non-provisional patent applications relating to our PCT and provisional patent applications, respectively, we cannot predict whether any such patent applications will result in the issuance of patents. If we or our licensors do not successfully obtain issued patents, or, if the scope of any patent protection we or our licensors obtain is not sufficiently broad, we will be unable to prevent others from using any product candidates we may develop or our technology or from developing or commercializing technology and products similar or identical to ours or other competing products and technologies. Any failure to obtain or maintain patent protection with respect to our ceDNA constructs, ctLNP delivery system, manufacturing processes or our other product candidates and technology would have a material adverse effect on our business, financial condition, results of operations and prospects.

The patent prosecution process is expensive, time-consuming and complex, and we and our licensors may not be able to file, prosecute, maintain, defend, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. We and our licensors may not be able to obtain, maintain or defend patents and patent applications due to the subject matter claimed in such patents and patent applications being in the public domain. For example, in some cases, the work of certain academic researchers in the genetic medicine field has entered or will enter the public domain, which may compromise our and our licensors' ability to obtain patent protection for certain inventions related to or building upon such prior work. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent

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protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach these agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Consequently, we would not be able to prevent any third party from using any of our technology that is in the public domain to compete with our product candidates.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has, in recent years, been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of patent rights are highly uncertain. Our pending and future owned and licensed patent applications may not result in patents being issued which protect our technology or product candidates, effectively prevent others from commercializing competitive technologies and product or otherwise provide any competitive advantage. In fact, patent applications may not issue as patents at all, and even if such patent applications do issue as patents, they may not issue in a form, or with a scope of claims, that will provide us with any meaningful protection, prevent others from competing with us or otherwise provide us with any competitive advantage. In addition, the scope of claims of an issued patent can be reinterpreted after issuance, and changes in either the patent laws or interpretation of the patent laws in the United States and other jurisdictions may diminish the value of our patent rights or narrow the scope of our patent protection. Furthermore, our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

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

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and other jurisdictions. For example, we may be subject to a third-party submission of prior art to the United States Patent and Trademark Office, or USPTO, challenging the validity of one or more claims of our owned or licensed patents. Such submissions may also be made prior to a patent's issuance, precluding the granting of a patent based on one of our owned or licensed pending patent applications. We may become involved in opposition, derivation, re-examination, *inter partes* review, post-grant review or interference proceedings and similar proceedings in foreign jurisdictions (for example, opposition proceedings) challenging our owned or licensed patent rights. In addition, a third party may claim that our owned or licensed patent rights are invalid or unenforceable in a litigation. An adverse result in any litigation or patent office proceeding could put one or more of our owned or licensed patents at risk of being invalidated, ruled unenforceable or interpreted narrowly and could allow third parties to commercialize products identical or similar to any product candidates we may develop and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Moreover, we, or one of our licensors, may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge priority of invention or other features of patentability. Such challenges and proceedings may result in loss of patent rights, exclusivity, freedom to

operate or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and any product candidates we may develop. Such challenges and proceedings may also result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. Moreover, there could be public announcements of the results of hearings, motions or other interim proceedings or developments related to such challenges and proceedings and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Furthermore, patents have a limited lifespan. In the United States, the expiration of a patent is generally 20 years from the earliest date of filing of the first non-provisional patent application to which the patent claims priority. Patent term adjustments and extensions may be available; however, the overall term of a patent, and the protection it affords, is limited. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent and other intellectual property rights may not provide us with sufficient rights to exclude others from commercializing products similar or identical to our technology and any product candidates we may develop. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

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

We are reliant upon licenses from third parties for certain patent and other intellectual property rights that are important or necessary to the development of our technology and product candidates. For example, we rely on a license from the National Institutes of Health, or NIH, and the Association Institut de Myologie, Universite Pierre et Marie Curie, Centre National de la Recherche Scientifique and Inserm Transfert SA, which we refer to as the French Institutions, pursuant to which we have been granted a non-exclusive, worldwide, royalty-bearing license to certain patent rights related to our ceDNA construct, to make and have made, research and have researched, use and have used, sell and have sold, offer to sell and to import products for the treatment, prevention or palliation of any human disease, disorder or condition. In addition, we rely on a license from UMass pursuant to which we have been granted an exclusive, worldwide, royalty-bearing license to certain patent rights related to our ceDNA construct to research, develop, manufacture, have manufactured, use, offer for sale, sell and import products in the treatment, prevention or palliation of any human disease, disorder or condition. Our existing license agreements, including our license agreements with NIH and UMass, impose, and we expect that future license agreements will impose, specified diligence, milestone payment, royalty, commercialization, development and other obligations on us and require us to meet development timelines, or to exercise diligent or commercially reasonable efforts to develop and commercialize licensed products, in order to maintain the licenses. For more information on the terms of the license agreements with NIH and UMass, see “Business—Intellectual property—License agreements.” We may enter into additional license agreements in the future.

Furthermore, the licensors of our license agreements have the right to terminate the agreement if we materially breach the agreement and fail to cure such breach within a specified period or in the event we undergo certain bankruptcy events. In spite of our best efforts, our current or any future licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements. If our license agreements are terminated, we may lose our rights to develop and commercialize any product candidates we may develop and technology, lose patent protection any product candidates we may develop and our technology, experience significant delays in the development and commercialization of our product candidates and

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technology and incur liability for damages. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, our competitors or other third parties could have the freedom to seek regulatory approval of, and to market, products and technologies identical or competitive to ours and we may be required to cease our development and commercialization of certain of our product candidates and technology. In addition, we may seek to obtain additional licenses from our licensors and, in connection with obtaining such licenses, we may agree to amend our existing licenses in a manner that may be more favorable to the licensors, including by agreeing to terms that could enable third parties, including our competitors, to receive licenses to a portion of the intellectual property that is subject to our existing licenses and to compete with any product candidates we may develop and our technology. Any of the foregoing could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

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

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

In addition, our license agreements are, and future license agreements are likely to be, complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our diligence, development, regulatory, commercialization, financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

If disputes over intellectual property that we have licensed or any other dispute described above related to our license agreements prevent or impair our ability to maintain our current license agreements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates and technology. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

Moreover, some of our in-licensed patent and other intellectual property rights are, and may in the future be, subject to third party interests such as co-ownership. If we choose not to or are unable to obtain an exclusive



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license to such third-party co-owners' interest, in such patent and other intellectual property rights, such third-party co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. We or our licensors may need the cooperation of any such co-owners of our licensed patent and other intellectual property rights in order to enforce them against third parties, and such cooperation may not be provided to us or our licensors.

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

Furthermore, our owned and in-licensed patent rights may be subject to a reservation of rights by one or more third parties. For example, inventions contained within some of our in-licensed patent rights may be made using U.S. government funding. When new technologies are developed with government funding, in order to secure ownership of patent rights related to the technologies, the recipient of such funding is required to comply with certain government regulations, including timely disclosing the inventions claimed in such patent rights to the U.S. government and timely electing title to such inventions. We rely on our licensors to ensure compliance with applicable obligations arising from such funding, including such timely disclosure and election of title. The failure of our licensors to meet their obligations may lead to a loss of rights or the unenforceability of relevant patents or patent applications. In addition, the U.S. government has certain rights in such in-licensed patent rights, including a non-exclusive license authorizing the U.S. government to use the invention or to have others use the invention on its behalf. If the U.S. government decides to exercise these rights, it is not required to engage us as its contractor in connection with doing so. The U.S. government's rights may also permit it to disclose the funded inventions and technology, which may include our confidential information, to third parties and to exercise march-in rights to use or allow third parties to use the technology we have licensed that was developed using U.S. government funding. The U.S. government may exercise its march-in rights if it determines that action is necessary because we or our licensors failed to achieve practical application of the U.S. government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such in-licensed U.S. government-funded inventions may be subject to certain requirements to manufacture any product candidates we may develop embodying such inventions in the United States. Any of the foregoing could harm our business, financial condition, results of operations and prospects significantly.

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

Filing, prosecuting, maintaining, enforcing and defending patents and other intellectual property rights on our technology and any product candidates we may develop in all jurisdictions throughout the world would be prohibitively expensive, and accordingly, our intellectual property rights in some jurisdictions outside the United States could be less extensive than those in the United States. In some cases, we or our licensors may not be able to obtain patent or other intellectual property protection for certain technology and product candidates outside the United States. In addition, the laws of some foreign jurisdictions do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we and our licensors may not be able to

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

Additionally, many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain jurisdictions, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement, misappropriation or other violation of our patent and other intellectual property rights or marketing of competing products in violation of our intellectual property rights generally. For example, an April 2019 report from the Office of the United States Trade Representative identified a number of countries, including China, Russia, Argentina, Chile and India, where challenges to the procurement and enforcement of patent rights have been reported. Proceedings to enforce our or our licensors' patent and other intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent and other intellectual property rights at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We or our licensors may not prevail in any lawsuits that we or our licensors 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.

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

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

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or patent applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned or licensed patent rights. We rely on our outside counsel and other professionals or our licensing partners to pay these fees due to the USPTO and non-U.S. government patent agencies. The USPTO and various non-U.S. government patent agencies also require compliance with several procedural, documentary and other similar provisions during the patent application process. We rely on our outside counsel and other professionals to help us comply and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. Moreover, complications due to the COVID-19 pandemic may result in inadvertent lapses due to, for example, unexpected closures of the USPTO or foreign patent offices, delays in delivery of notifications relating to deadlines, or failure to timely and/or properly obtain signatures on necessary documents. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment, loss of priority or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an

event, potential competitors might be able to enter the market and this circumstance could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

***We may not be successful in obtaining necessary rights to product candidates we may develop through acquisitions and in-licenses.***

We currently have rights to certain intellectual property through licenses from third parties. Because our programs may require the use of additional intellectual property rights held by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these intellectual property rights. In addition, with respect to any patent or other intellectual property rights that we co-own with third parties, we may require exclusive licenses to such co-owners' interest in such patent or other intellectual property rights. However, we may be unable to secure such licenses or otherwise acquire or in-license any intellectual property rights related to compositions, methods of use, processes or other components from third parties that we identify as necessary for any product candidates we may develop and our technology on commercially reasonable terms, or at all. Even if we are able to in-license any such necessary intellectual property, it could be on non-exclusive terms, thereby giving our competitors and other third parties access to the same intellectual property licensed to us, and the applicable licensors could require us to make substantial licensing and royalty payments. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

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

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

***Issued patents covering any product candidates we may develop could be found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad.***

Our owned and licensed patent rights may be subject to priority, validity, inventorship and enforceability disputes. If we or our licensors are unsuccessful in any of these proceedings, such patent rights may be narrowed, invalidated or held unenforceable, we may be required to obtain licenses from third parties, which may not be available on commercially reasonable terms or at all, or we may be required to cease the development, manufacture and commercialization of one or more of our product candidates. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

If one of our licensing partners, one of our co-owners, we or our licensor's other licensees initiate legal proceedings against a third party to enforce a patent covering any of any product candidates we may develop or our technology, the defendant could counterclaim that the patent covering the product candidate or technology is

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

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

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, contractors and other parties who have access to such technology and processes. However, we may not be able to prevent the unauthorized disclosure or use of our technical know-how or other trade secrets by the parties to these agreements. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees and consultants who are parties to these agreements breach or violate the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. As a result, we could lose our trade secrets and third parties could use our trade secrets to compete with any product candidates we may develop and our technology. Additionally, we cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology and processes.

We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems; however, such systems and security measures may be breached, and we may not have adequate remedies for any breach.

In addition, our trade secrets may otherwise become known or be independently discovered by competitors or other third parties. Competitors or third parties could purchase any product candidates we may develop or our technology and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our intellectual property rights or develop their own competitive technologies that fall outside the scope of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate such trade secrets, from using that technology or information to compete with us. If our trade secrets are not adequately protected so as to protect our market against competitors' products, our business, financial condition, results of operations and prospects could be materially and adversely affected.

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may become party to, or be threatened with, adversarial proceedings or litigation in which third parties may assert infringement, misappropriation or other violation claims against us, alleging that any product candidates we may develop, manufacturing methods, formulations or administration methods are covered by their patents. Given the vast number of patents and other intellectual property in our field of technology, we cannot be certain or guarantee that we do not infringe, misappropriate or otherwise violate patents or other intellectual property. Other companies and institutions have filed, and continue to file, patent applications that may be related to our technology and, more broadly, to gene therapy and related manufacturing methods. Some of these patent applications have already been allowed or issued and others may issue in the future. Since this area is competitive and of strong interest to pharmaceutical and biotechnology companies, there will likely be additional patent applications filed and additional patents granted in the future, as well as additional research and development programs expected in the future. If a patent holder believes the manufacture, use, sale or importation of any product candidates we may develop or our technology infringes its patent, the patent holder may sue us even if we have licensed other patent rights for our technology.

It is also possible that we have failed to identify relevant third-party patents or applications. Because patent applications can take many years to issue, may be confidential for 18 months or more after filing and can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use, sale or importation of any product candidates we may develop or our technology and we may not be aware of such patents. Furthermore, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States may remain confidential until a patent issues. Moreover, it is difficult for industry participants, including us, to identify all third-party patent rights that may be relevant to any product candidates we may develop and our technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, any product candidates we may develop or the use of any product candidates we may develop.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could adversely affect our ability to commercialize any product candidates we may develop or any other of our product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing any product candidates we may develop and our technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same

technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidates. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing any product candidates we may develop or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

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

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

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors or other third parties may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could adversely affect our ability to compete in the marketplace and could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or be required to obtain licenses to such intellectual property rights, which may not be available on commercially reasonable terms or at all. An inability to incorporate such intellectual property rights would harm our business and may prevent us from successfully commercializing any product candidates we may develop or at all. In addition, we may lose personnel as a result of such claims and any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent contractors. A loss of key personnel or their work product could hamper or prevent our ability to commercialize any product candidates we may develop and our technology, which would have a material adverse effect on our business, results of operations, financial condition and prospects. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our scientific and management personnel.

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. Moreover, even when we obtain agreements assigning intellectual property to us, 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. Furthermore, individuals executing agreements with us may have pre-existing or competing obligations to a third party, such as an academic institution, and thus an agreement with us may be ineffective in perfecting ownership of inventions developed by that individual. Disputes about the ownership of intellectual property that we own may have a material adverse effect on our business, financial condition, results of operations and prospects.

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

***Changes in patent law in the United States or worldwide could diminish the value of patents in general, thereby impairing our ability to protect any product candidates we may develop and our technology.***

Changes in either the patent laws or interpretation of patent laws in the United States and worldwide, including patent reform legislation such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, could increase the uncertainties and costs surrounding the prosecution of any owned or in-licensed patent applications and the maintenance, enforcement or defense of any current in-licensed issued patents and issued patents we may own or in-license in the future. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which, assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our in-licensed issued patents and issued patents we may own or in-license in the future, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. As one example, in the case *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court held that certain claims to DNA molecules are not patentable simply because they have been isolated from surrounding material. Moreover, in 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 patent-ineligible subject matter. Accordingly, in view of the guidance memo, there can be no assurance that claims in our patent rights covering any product candidates we may develop or our technology will be held by the USPTO or equivalent foreign patent offices or by courts in the United States or in foreign jurisdictions to cover patentable subject matter. This combination of events has created uncertainty with respect to the validity and enforceability of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future.

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

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop and our technology, one or more of our U.S. patents that we license or may own in the future may be eligible for limited patent term extension under 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 product, a method for using it or a method for manufacturing it may be extended. The application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. 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. In addition, to the extent we wish to pursue patent term extension based on a patent that we in-license from a third party, we would need the cooperation of that third party. 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. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patent rights, trade secrets or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates or technology. Litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in-licensed patent rights, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of or right to use intellectual property that is important to any product candidates we may develop or our technology. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

We have filed trademark applications with the USPTO for the mark "Generation Bio" and the Generation Bio logo. Our current and future trademark applications in the United States and other foreign jurisdictions may not



be allowed or may be subsequently opposed. Once filed and registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. As a means to enforce our trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition proceedings. This can be expensive and time-consuming, particularly for a company of our size. 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, third parties 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. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations or prospects.

***Intellectual property rights do not necessarily address all potential threats.***

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

- others may be able to make gene therapy products that are similar to any product candidates we may develop but that are not covered by the intellectual property, including the claims of the patents, that we own or license currently or in the future;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or license currently or in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating our owned or licensed intellectual property rights;
- it is possible that our or our licensors' current or future pending patent applications will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by third parties;
- third parties might conduct research and development activities in jurisdictions where we do not have patent or other intellectual property rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents or other intellectual property rights of others may have an adverse effect on our business; and
- we may choose not to file a patent for certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

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

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

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

#### **Risks related to regulatory approval and other legal compliance matters**

***Regulatory requirements governing genetic medicine products, and in particular any novel gene therapy products we may develop, have changed frequently and may continue to change in the future.***

Regulatory requirements governing gene and cell therapy products, and in particular any novel gene therapy products we may develop, have changed frequently and may continue to change in the future. We are aware of a limited number of gene therapy products that have received marketing authorization from the FDA and EMA. Even with respect to more established products in the gene therapy field, the regulatory landscape is still developing. For example, the FDA has established the Office of Tissues and Advanced Therapies (formerly the Office of Cellular, Tissue and Gene Therapies) within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the NIH also are potentially subject to review by the Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC; however, the NIH announced that the RAC will only publicly review clinical trials if the trials cannot be evaluated by standard oversight bodies and pose unusual risks.

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

These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of any

product candidates we may develop or lead to significant post-approval limitations or restrictions. As we advance any product candidates we may develop, 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 these product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue to maintain our business.

Although the FDA decides whether individual genetic medicine protocols may proceed, the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if the FDA has reviewed the trial design and details and approved its initiation. Conversely, the FDA can put an IND on a clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. If we were to engage an NIH-funded institution to conduct a clinical trial, that institution's IBC as well as its IRB would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of genetic medicine products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any product candidates we may develop. Similarly, the EMA may issue new guidelines concerning the development and marketing authorization for genetic medicine products and require that we comply with these new guidelines.

As we are initially seeking to identify and develop product candidates to treat diseases using novel technologies, there is heightened risk that the FDA, the EMA or other regulatory authority may not consider the clinical trial endpoints that we propose to provide clinically meaningful results. Even if the endpoints are deemed clinically meaningful, we may not achieve these endpoints to a degree of statistical significance, particularly because many of the diseases we are targeting with our platform have small patient populations, making development of large and rigorous clinical trials more difficult.

Adverse developments in post-marketing experience or in clinical trials conducted by others of gene therapy products or cell therapy products may cause the FDA, the EMA, and other regulatory bodies to revise the requirements for development or approval of any product candidates we may develop or limit the use of products utilizing non-viral gene therapy technologies, either of which could materially harm our business. In addition, the clinical trial requirements of the FDA, the EMA, and other 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 the potential products. The regulatory approval process for novel product candidates such as the product candidates we may develop can be more expensive and take longer than for other, better known or more extensively studied pharmaceutical or other product candidates. Regulatory agencies administering existing or future regulations or legislation may not allow production and marketing of products utilizing non-viral gene therapy technology in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays or other impediments to our research programs or the commercialization of resulting products.

In addition, ethical, social and legal concerns about genetic medicine, genetic testing and genetic research could result in additional regulations or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed their intentions to further regulate biotechnology. More restrictive regulations or claims that any product candidates we may develop 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 any product candidates we may develop under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

As we advance any product candidates we may develop through clinical development, we will be required to consult with these regulatory and advisory groups, and comply with applicable guidelines. These regulatory review committees and advisory groups and any new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of any product

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candidates we may develop or lead to significant post-approval limitations or restrictions. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue.

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

Any product candidates we may develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate we may develop will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CLROs to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information, including manufacturing information, to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity and potency. Any product candidates we may develop may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities, or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved medicine not commercially viable.

Finally, disruptions at the FDA and other agencies may prolong 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 employees and stop critical 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. The Trump Administration also took several executive actions that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities.

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

***Negative public opinion of gene therapy and increased regulatory scrutiny of gene therapy and genetic research may adversely impact public perception of our future product candidates.***

Our potential therapeutic products involve introducing genetic material into patients' cells. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene therapy and gene regulation for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy and gene regulation are unsafe, unethical or immoral, and, consequently, our products may not gain the acceptance of the public or the medical community. Adverse public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar and for which greater clinical data may be available.

More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products once approved. For example, in 2003, trials using early versions of murine gamma-retroviral vectors, which integrate with, and thereby alter, the host cell's DNA, have led to several well-publicized adverse events, including reported cases of leukemia. Although our delivery system is non-viral, any product candidates we may develop may be associated with such viral delivery systems as a gene therapy platform. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. The risk of cancer remains a concern for gene therapy and we cannot assure that it will not occur in any of our planned or future clinical trials. In addition, there is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biological activity of the genetic material or other components of products used to carry the genetic material. If any such adverse events occur, commercialization of our product candidates or further advancement of our clinical trials could be halted or delayed, which would have a negative impact on our business and operations.

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

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

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the recent withdrawal of the United Kingdom from the European Union, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the European Union, the United Kingdom withdrew from the European Union, effective December 31, 2020. On December 24, 2020, the United Kingdom and European Union entered into a Trade and Cooperation Agreement. The agreement sets out certain procedures for approval and recognition of medical products in each jurisdiction.

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Since the regulatory framework for pharmaceutical products in the United Kingdom covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing any product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for any product candidates, which could significantly and materially harm our business.

***A Fast Track, Breakthrough Therapy or Priority Review designation by the FDA may not lead to a faster development or regulatory review or approval process, and does not assure FDA approval of our product candidates.***

If a product candidate is intended for the treatment of a serious or life-threatening condition and the product candidate demonstrates the potential to address unmet medical need for this condition, the sponsor may apply to the FDA for fast track designation. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective.

In addition, an applicant may seek designation of its product as a breakthrough therapy, which is a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug 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 drugs and biologics 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.

Further, if the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months.

We may seek these and other designations for our product candidates. The FDA has broad discretion with respect to whether or not to grant these designations to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a fast track or breakthrough therapy designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. As a result, while we may seek and receive these designations for our product candidates, we may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw these designations if it believes that the designation is no longer supported by data from our clinical development program.

***We may not be able to obtain orphan drug exclusivity for any product candidates we may develop, and even if we do, that exclusivity may not prevent the FDA or the EMA from approving other competing products.***

Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition. A similar regulatory scheme governs approval of orphan products by

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the EMA in the European Union. Generally, if a product candidate with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for the same product for the same therapeutic indication for that time period. The applicable period is seven years in the United States and ten years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation, in particular if the product is sufficiently profitable so that market exclusivity is no longer justified.

In order for the FDA to grant orphan drug exclusivity to one of our products, the agency must find that the product is indicated for the treatment of a condition or disease with a patient population of fewer than 200,000 individuals annually in the United States. The FDA may conclude that the condition or disease for which we seek orphan drug exclusivity does not meet this standard. Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. In particular, the concept of what constitutes the “same drug” for purposes of orphan drug exclusivity remains in flux in the context of gene therapies, and the FDA has issued recent draft guidance suggesting that it would not consider two genetic medicine products to be different drugs solely based on minor differences in the transgenes or vectors. In addition, even after an orphan drug is approved, the FDA can subsequently approve the same product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of the patients with the rare disease or condition.

In 2017, the Congress passed the FDARA. FDARA, among other things, codified the FDA’s pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. Under Omnibus legislation signed by President Trump on December 27, 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of FDARA in 2017, but have not yet been approved or licensed by the FDA. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

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

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if any product candidates we may develop demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. Regulatory agencies also may approve a product 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 any product candidates we may develop. For example, our development of any product candidates for pediatric use is an important part of our current business strategy, and if we are unable to obtain regulatory approval for the desired age ranges, our business may suffer.

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

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The FDA typically advises that patients treated with genetic medicine undergo follow-up observations for potential adverse events for a 15-year period. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine.

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

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

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

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

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

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of medicines to ensure that they are marketed only for the approved indications and in accordance with the provisions of the



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approved labeling. The FDA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our medicines for their approved indications, we may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the Department of Justice. Violation of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may also lead to investigations or allegations of violations of federal and state healthcare fraud and abuse laws and state consumer protection laws.

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

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

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

Additionally, if any product candidates we may develop receive 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 and a communication plan to healthcare practitioners. Furthermore, if we or others later identify undesirable side effects caused by our product candidate, several potentially significant negative consequences could result, including:

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

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

Healthcare providers, physicians and third-party payers play a primary role in the recommendation and prescription of any product candidates that we develop for which we obtain marketing approval. Our future

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arrangements with third-party payers and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order, or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid or other government payers that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties;
- HIPAA, as further amended by the Health Information Technology for Economic and Clinical Health Act, which imposes certain requirements, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, healthcare clearinghouses and healthcare providers;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements under the federal Physician Payment Sunshine Act, which requires manufacturers of drugs, devices, biologics and medical supplies to report to HHS, information related to payments and other transfers of value to physicians and teaching hospitals and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers, and certain state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures.

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. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, imprisonment and the curtailment or restructuring of our operations, any of which could adversely affect our business, financial condition, results of operations and prospects.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs,

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

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

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

In March 2010, the United States Congress enacted PPACA. In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2029 unless additional Congressional action is taken. The CARES Act suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the PPACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Act, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the PPACA is an essential and inseparable feature of the PPACA, and therefore because the mandate was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. On December 18, 2019, the Court of Appeals for the Fifth Circuit court affirmed the lower court's ruling that the individual mandate portion of the PPACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the PPACA. Thereafter, the U.S. Supreme Court agreed to hear this case. Oral argument in the case took place on November 10, 2020. On February 10, 2021, the Biden Administration withdrew the federal government's support for overturning the PPACA. A ruling by the Court is expected sometime this year. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

The Trump Administration also took executive actions to undermine or delay implementation of the PPACA, including directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of

pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new executive order which directs federal agencies to reconsider rules and other policies that limit Americans' access to healthcare, and consider actions that will protect and strengthen that access. Under this order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the PPACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and under the PPACA; and policies that reduce affordability of coverage or financial assistance, including for dependents. This executive order also directs the U.S. Department of Health and Human Services to create a special enrollment period for the Health Insurance Marketplace in response to the COVID-19 pandemic.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates.

***The prices of prescription pharmaceuticals in the United States and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our products, if and when licensed.***

The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. To date, there have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for products. To those ends, President Trump issued several executive orders intended to lower the costs of prescription drug products. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing President Trump's most favored nation model, but such final rule is currently subject to a nationwide preliminary injunction. It remains to be seen whether these orders and resulting regulations will remain in force during the Biden Administration. Further, on September 24, 2020, the Trump Administration finalized a rulemaking allowing states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants are required to demonstrate that their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. The FDA has issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

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

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In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In markets outside of the United States and the European Union, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

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

We are exposed to the risk of fraud or other misconduct by our employees, consultants and partners, and, if we commence clinical trials, our principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union and other jurisdictions, provide accurate information to the FDA, the European Commission and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately, or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations and prospects, including the imposition of significant fines or other sanctions.

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

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

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

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Compliance with the FCPA and other anti-corruption laws potentially applicable to our business is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, compliance with the FCPA and other anti-corruption laws presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions. Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products.

Our expansion outside of the United States has required, and will continue to require, us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain drugs and drug candidates outside of the United States, which could limit our growth potential and increase our development costs. For example, the provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is prohibited in the European Union. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of European Union member states and the UK Bribery Act 2010. Violation of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain European Union member states must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union member states. These requirements are provided in the national laws, industry codes or professional codes of conduct applicable in the European Union member states. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

The failure to comply with laws governing international business practices may result in substantial penalties, including suspension or debarment from government contracting. Violation of the FCPA can result in significant civil and criminal penalties. Indictment alone under the FCPA can lead to suspension of the right to do business with the U.S. government until the pending claims are resolved. Conviction of a violation of the FCPA can result in long-term disqualification as a government contractor. The termination of a government contract or relationship as a result of our failure to satisfy any of our obligations under laws governing international business practices would have a negative impact on our operations and harm our reputation and ability to procure government contracts. The SEC also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

***We are subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies, contractual obligations and failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.***

We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally-identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, claims for damages by affected individuals, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer or other processing of personal

data regarding individuals in the European Union, including personal health data, is subject to the European Union General Data Protection Regulation (EU) 2016/679, or the GDPR, which took effect across all member states of the EEA in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States and, as a result, increases the scrutiny that such rules should apply to transfers of personal data from clinical trial sites located in the EEA to the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of the GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. In addition, the GDPR provides that European Union member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

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

Similar privacy and data security requirements are either in place or underway in the United States. There are a broad variety of data protection laws that may be applicable to our activities, and a range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act of 2018, or the CCPA, which became effective on January 1, 2020, requires companies that process information on California residents to make new disclosures to consumers about their data collection, use and sharing practices, allow consumers to opt out of certain data sharing with third parties and provide a new cause of action for data breaches. Additionally, effective starting on January 1, 2023, the California Privacy Rights Act, or the CPRA, will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. Many other states are considering similar legislation, and a broad range of legislative measures also have been introduced at the federal level.

There are numerous U.S. federal and state laws and regulations related to the privacy and security of personal information, including certain laws that regulate the use and disclosure of personal health information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information, and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. These provisions may be applicable to our business in the future. Determining whether protected

health information has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation.

If we are unable to properly protect the privacy and security of protected health information, we could be found to have violated these privacy and security laws and/or breached certain contracts with our business partners. Further, if we fail to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, we could face civil and criminal penalties. HHS enforcement activity can result in financial liability and reputational harm, and responses to such enforcement activity can consume significant internal resources. In addition, state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. We cannot be sure how these regulations will be interpreted, enforced or applied to our operations. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems.

It is possible that new and existing laws may be interpreted and applied in a manner that is inconsistent with our practices and our efforts to comply with the evolving data protection rules may be unsuccessful. If so, this could result in government-imposed fines or penalties or orders requiring that we change our practices, which could adversely affect our business. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with federal, state and international laws regarding privacy and security of personal information could expose us to fines and penalties under such laws. Any such failure to comply with data protection and privacy laws could result in government-imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. We also face a threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business, financial condition, results of operations or prospects.

#### **Risks related to employee matters and managing growth**

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

We are highly dependent on the research and development, clinical, financial, operational and other business expertise of our executive officers, as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment offer letters with our executive officers, each of them may terminate their employment with us at any time. We do not maintain “key person” insurance for any of our executives or other employees. Recruiting and retaining qualified scientific, clinical, manufacturing, accounting, legal and sales and marketing personnel will also be critical to our success.

The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. Our success as a public company also depends on implementing and maintaining internal controls and the



accuracy and timeliness of our financial reporting. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

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

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

As a growing biotechnology company, we are actively pursuing new platforms and product candidates in many therapeutic areas and across a wide range of diseases. Successfully developing product candidates for and fully understanding the regulatory and manufacturing pathways to all of these therapeutic areas and disease states requires a significant depth of talent, resources and corporate processes in order to allow simultaneous execution across multiple areas. Due to our limited resources, we may not be able to effectively manage this simultaneous execution and the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, legal or regulatory compliance failures, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to compete effectively and commercialize our product candidates, if approved, will depend in part on our ability to effectively manage the future development and expansion of our company.

***Future acquisitions or strategic alliances could disrupt our business and harm our financial condition and results of operations.***

We may acquire additional businesses or drugs, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new drugs resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure our stockholders that, following any such acquisition, we will achieve the expected synergies to justify the transaction. The risks we face in connection with acquisitions, include:

- diversion of management time and focus from operating our business to addressing acquisition integration challenges;
- coordination of research and development efforts;
- retention of key employees from the acquired company;
- changes in relationships with strategic partners as a result of product acquisitions or strategic positioning resulting from the acquisition;

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- cultural challenges associated with integrating employees from the acquired company into our organization;
- the need to implement or improve controls, procedures and policies at a business that prior to the acquisition may have lacked sufficiently effective controls, procedures and policies;
- liability for activities of the acquired company before the acquisition, including intellectual property infringement claims, violation of laws, commercial disputes, tax liabilities and other known liabilities;
- unanticipated write-offs or charges; and
- litigation or other claims in connection with the acquired company, including claims from terminated employees, customers, former stockholders or other third parties.

Our failure to address these risks or other problems encountered in connection with our past or future acquisitions or strategic alliances could cause us to fail to realize the anticipated benefits of these transactions, cause us to incur unanticipated liabilities and harm the business generally. There is also a risk that future acquisitions will result in the incurrence of debt, contingent liabilities, amortization expenses or incremental operating expenses, any of which could harm our financial condition or results of operations.

***Our internal information technology systems, or those of our third-party vendors, collaborators or other contractors or consultants, may fail or suffer security breaches, loss or leakage of data and other disruptions, which could result in a material disruption of our product development programs, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability or otherwise adversely affecting our business.***

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information.

Despite the implementation of security measures, given the size and complexity of our internal information technology systems and those of our current and any future third-party vendors, collaborators and other contractors and consultants, and the increasing amounts of confidential information that they maintain, such information technology systems are vulnerable to damage or interruption from computer viruses, computer hackers, malicious code, employee theft or misuse, denial-of-service attacks, sophisticated nation-state and nation-state-supported actors, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. We may not be able to anticipate all types of security threats, and we may not be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies.

While we seek to protect our information technology systems from system failure, accident and security breach, if such an event were to occur and cause interruptions in our operations, it could result in a disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary or confidential information or other disruptions. For example, the loss of clinical trial data from future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. If we were to experience a significant cybersecurity breach of our information systems or data, the costs associated with the investigation, remediation and potential notification of the breach to counterparties and data subjects could be material. In addition, our remediation efforts may not be successful. Moreover, if the information technology systems of our third-party vendors, collaborators and other contractors and consultants become subject to disruptions or security breaches, we may have insufficient recourse against

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such third parties and we may have to expend significant resources to mitigate the impact of such an event, and to develop and implement protections to prevent future events of this nature from occurring. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information.

To the extent that any disruption or security breach were to result in a loss of, or damage to, our or our third-party vendors', collaborators' or other contractors' or consultants' data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability including litigation exposure, penalties and fines, we could become the subject of regulatory action or investigation based primarily on the laws and regulations discussed above in the privacy discussion, our competitive position and reputation could be harmed and the further development and commercialization of our product candidates could be delayed. Furthermore, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our customers or employees, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages. Any of the above could have a material adverse effect on our business, financial condition, results of operations or prospects.

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

We depend on our employees, consultants, CDMOs, CLROs, as well as regulatory agencies and other parties, for the continued operation of our business. While we maintain disaster recovery plans, they might not adequately protect us. Despite any precautions we take for natural disasters or other catastrophic events, these events, including terrorist attack, pandemics, hurricanes, fire, floods and ice and snowstorms, could result in significant disruptions to our research and development, preclinical studies, clinical trials, and, ultimately, commercialization of our products. Long-term disruptions in the infrastructure caused by events, such as natural disasters, the outbreak of war, the escalation of hostilities and acts of terrorism or other "acts of God," particularly involving cities in which we have offices, manufacturing or clinical trial sites, could adversely affect our businesses. Although we carry business interruption insurance policies and typically have provisions in our contracts that protect us in certain events, our coverage might not respond or be adequate to compensate us for all losses that may occur. Any natural disaster or catastrophic event affecting us, our CDMOs, our CLROs, regulatory agencies or other parties with which we are engaged could have a significant negative impact on our operations and financial performance.

### **Risks related to ownership of our common stock and our status as a public company**

#### ***We do not know whether a market will continue to develop or be sustained for our common stock, and, as a result, it may be difficult for our stockholders to sell their shares of our common stock.***

Although our common stock is listed on the Nasdaq Global Select Market, an active trading market for our shares may not continue to develop or be sustained. As a result, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or at all.

#### ***The price of our common stock is volatile and fluctuates substantially, which could result in substantial losses for purchasers of our common stock.***

Our stock price has been, and is likely to continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, our stockholders

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may not be able to sell their common stock at or above the price they paid for their shares. The market price for our common stock may be influenced by many factors, including:

- results of or developments in preclinical studies and clinical trials of any product candidates we may develop or those of our competitors or potential collaborators;
- timing of the results of our preclinical studies and clinical trials or those of our competitors;
- our success in commercializing any product candidates we may develop, if and when approved;
- the success of competitive products or technologies;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other intellectual property or proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any product candidates we may develop;
- the results of our efforts to discover, develop, acquire or in-license products, product candidates, technologies or data referencing rights, the costs of commercializing any such products and the costs of development of any such product candidates or technologies;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or the financial results of companies that are perceived to be similar to us;
- sales of common stock by us, our executive officers, directors or principal stockholders or others;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry, political and market conditions; and
- the other factors described in this “Risk Factors” section.

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

***If securities analysts do not publish or cease publishing research or reports or publish misleading, inaccurate or unfavorable research about our business or if they publish negative evaluations of our stock, the price and trading volume of our stock could decline.***

The trading market for our common stock relies, in part, on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts covering our business downgrade their evaluations of our stock or publish inaccurate or unfavorable research about our business, or provide more favorable relative recommendations about our competitors, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

***The COVID-19 pandemic, which began in late 2019 and was declared a global pandemic by the World Health Organization in March 2020, may affect our ability to initiate and complete preclinical studies, delay the initiation of our planned clinical trial or future clinical trials, disrupt regulatory activities, or have other adverse effects on our business and operations. In addition, this pandemic has caused substantial disruption in the financial markets and may adversely impact economies worldwide, each of which could result in adverse effects on our business, on raising capital and on our operations.***

The COVID-19 pandemic, which began in December 2019 and was declared a global pandemic by the World Health Organization in March 2020, has caused and continues to cause many governments to implement measures to slow the spread of the outbreak through quarantines, travel restrictions, heightened border scrutiny and other measures. The outbreak and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. The future progression of the outbreak and its effects on our business and operations continue to be uncertain. We and our CDMOs and CROs experienced a temporary reduction in the capacity to undertake research-scale production and to execute some preclinical studies, and may face disruptions in the future that affect our ability to initiate and complete preclinical studies, and disruptions in procuring items that are essential for our research and development activities, such as raw materials used in the manufacture of any product candidates we may develop, laboratory supplies used in our preclinical studies, or animals that are used for preclinical testing for which there are shortages because of ongoing efforts to address the outbreak. We and our CROs and CDMOs may also face disruptions related to our future IND-enabling studies and clinical trials arising from delays in preclinical studies, manufacturing disruptions, and the ability to obtain necessary IRB, IBC or other necessary site approvals, as well as other delays at clinical trial sites. The response to the COVID-19 pandemic may redirect resources with respect to regulatory and intellectual property matters in a way that would adversely impact our ability to progress regulatory approvals and protect our intellectual property. In addition, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions. The pandemic has caused significant disruptions in the financial markets, and may continue to cause such disruptions, which may impact the volatility of our stock price and trading in our stock. Moreover, the pandemic has significantly impacted economies worldwide, which could result in adverse effects on our business and operations. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business and it has the potential to adversely affect our business, financial condition, results of operations and prospects.

***Unfavorable global economic conditions could adversely affect our business, financial condition, stock price and 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 2008 global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the 2008 global financial crisis, could result in a variety of risks to our business, including, weakened demand for any product candidates we may develop 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. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive such difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget. 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. Furthermore, our stock price may decline due in part to the volatility of the stock market and any general economic downturn.

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

As of February 28, 2021, our executive officers and directors and their affiliates, in the aggregate, beneficially owned shares representing approximately 26% of our common stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets.

This concentration of ownership may:

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

***We have broad discretion in the use of cash, cash equivalents and marketable securities and may not use them effectively.***

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

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

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

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

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock and make it more difficult for our stockholders to sell their common stock at a time and price that they deem appropriate. As of February 28, 2021, we had 56,427,399 shares of common stock outstanding. In connection with our follow-on public offering, we and each our directors and executive officers and certain of our stockholders entered into lock-up agreements. As of February 28, 2021, 14,230,587 shares of common stock are restricted as a result of these lock-up agreements, which, subject to certain specified exceptions, will become eligible to be sold after the expiration of the lock-up period on April 7, 2021. The representatives of the underwriters may release some or all of the shares of common stock subject to lock-up agreements at any time in their sole discretion and without notice, which would allow for earlier sales of shares in the public market.

In addition, certain of our executive officers, directors and affiliated stockholders have entered or may enter into Rule 10b5-1 plans providing for sales of shares of our common stock from time to time. Under a Rule 10b5-1 plan, a broker executes trades pursuant to parameters established by the executive officer, director or affiliated stockholder when entering into the plan, without further direction from the executive officer, director or affiliated stockholder. A Rule 10b5-1 plan may be amended or terminated in some circumstances. Our executive officers, directors and affiliated stockholders also may buy or sell additional shares outside of a Rule 10b5-1 plan when they are not in possession of material, nonpublic information.

Moreover, as of February 28, 2021, holders of an aggregate of 22,972,666 shares of our common stock had rights, along with holders of an additional 450,076 shares of our common stock issuable upon exercise of outstanding options, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We have also filed a registration statement on Form S-8 to register all of the shares of common stock that we were able to issue under our equity compensation plans as of December 31, 2020, and we intend to file a registration statement on Form S-8 to register the additional 2,348,500 shares of our common stock that became issuable under our equity compensation plans on January 1, 2021. Shares registered under these registration statements on Form S-8 can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates, vesting arrangements and exercise of options, and the lock-up agreements entered into in connection with our follow-on public offering.

***We are an “emerging growth company,” and a “smaller reporting 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 Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may remain an EGC until December 31, 2025, although if the market value of our common stock that is held by non-affiliates exceeds \$700.0 million as of any June 30 before that time or if we have annual gross revenues of \$1.07 billion or more in any fiscal year, we would cease to be an EGC as of December 31 of the applicable year. We also would cease to be an EGC if we issue more than \$1.0 billion of non-convertible debt over a three-year period. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not EGCs. These exemptions include:

- being permitted to provide only two years of audited financial statements in this Annual Report, in addition to any required unaudited interim financial statements, with correspondingly reduced “Management’s discussion and analysis of financial condition and results of operations” disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

Even after we no longer qualify as an emerging growth company, we may continue to qualify as a “smaller reporting company,” which would allow us to take advantage of many of the same exemptions from disclosure requirements, including reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. In addition, if we are a smaller reporting company with less than \$100 million in annual revenue, we would not be required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404. In reliance on these exemptions, we have taken advantage of reduced reporting obligations in this Annual Report. In particular, in this Annual Report, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an EGC or a smaller reporting company.

We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

In addition, the JOBS Act permits an EGC to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to

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

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

As a public company we incur, and particularly after we are no longer an EGC or a smaller reporting company, we will further incur, significant legal, accounting and other expenses that we did not previously incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote and will continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs, particularly as we hire additional financial and accounting employees to meet public company internal control and financial reporting requirements and will make some activities more time-consuming and costly compared to when we were a private company.

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

Pursuant to Section 404, we will be required to furnish a report by our management on our internal control over financial reporting beginning with our filing of an Annual Report on Form 10-K with the SEC for the year ended December 31, 2021. However, while we remain an EGC or a smaller reporting company with less than \$100 million in annual revenue, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, including through hiring additional financial and accounting personnel, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses in our internal control over financial reporting, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement



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

We are required to disclose changes made in our internal controls and procedures on a quarterly basis and our management is required to assess the effectiveness of these controls annually. However, for as long as we are an EGC under the JOBS Act or a smaller reporting company, 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. 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, which could have a negative effect on the trading price of our stock.

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

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

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

Recent changes in tax law may adversely affect our business or financial condition. On December 22, 2017, the U.S. government enacted the Tax Act, which significantly reformed the Code. The Tax Act, among other things, contained significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), the limitation of the deduction for NOLs arising in taxable years beginning after December 31, 2017 to 80% of current year taxable income and elimination of NOL carrybacks for losses arising in taxable years ending after December 31, 2017 (though any such NOLs may be carried forward indefinitely), the imposition of a one-time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, the elimination of U.S. tax on foreign earnings (subject to certain important exceptions), the allowance of immediate deductions for certain new investments instead of deductions for depreciation expense over time, and the modification or repeal of many business deductions and credits.

As part of Congress' response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020, and the CARES Act was enacted on March 27, 2020 and COVID relief provisions were included in the Consolidated Appropriations Act, 2021 or CAA, which was enacted on December 27, 2020. All contain numerous tax provisions. In particular, the CARES Act retroactively and temporarily (for taxable years beginning before January 1, 2021) suspends application of the 80%-of-income limitation on the use of NOLs, which was enacted as part of the Tax Act. It also provides that NOLs arising in

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any taxable year beginning after December 31, 2017, and before January 1, 2021 are generally eligible to be carried back up to five years. The CARES Act also temporarily (for taxable years beginning in 2019 or 2020) relaxes the limitation of the tax deductibility for net interest expense by increasing the limitation from 30% to 50% of adjusted taxable income.

Regulatory guidance under the Tax Act, the FFCR Act, the CARES Act and the CAA is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. Congress may enact additional legislation in connection with the COVID-19 pandemic, and as a result of the changes in the U.S. presidential administration and control of the U.S. Senate, additional tax legislation may also be enacted; any such additional legislation could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the FFCR Act, the CARES Act or the CAA.

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

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

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

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

### ***Our restated certificate of incorporation designates the state courts in the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against the company and our directors, officers and employees.***

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of

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Delaware does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for the following types of proceedings:

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

These choice of forum provisions will not apply to suits brought to enforce a duty or liability created by the Securities Act of 1933, as amended, or the Securities Act, the Exchange Act or any other claim for which federal courts have exclusive jurisdiction. Furthermore, our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act.

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

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

We depend on our employees, consultants, CDMOs, CLROs, as well as regulatory agencies and other parties, for the continued operation of our business. While we maintain disaster recovery plans, they might not adequately protect us. Despite any precautions we take for natural disasters or other catastrophic events, these events, including terrorist attack, pandemics, hurricanes, fire, floods and ice and snowstorms, could result in significant disruptions to our research and development, preclinical studies, clinical trials, and, ultimately, commercialization of our products. Long-term disruptions in the infrastructure caused by events, such as natural disasters, the outbreak of war, the escalation of hostilities and acts of terrorism or other “acts of God,” particularly involving cities in which we have offices, manufacturing or clinical trial sites, could adversely affect our businesses. Although we carry business interruption insurance policies and typically have provisions in our contracts that protect us in certain events, our coverage might not respond or be adequate to compensate us for all losses that may occur. Any natural disaster or catastrophic event affecting us, our CDMOs, our CLROs, regulatory agencies or other parties with which we are engaged could have a significant negative impact on our operations and financial performance.

**ITEM 1B. UNRESOLVED STAFF COMMENTS**

None.

**ITEM 2. PROPERTIES**

Our headquarters are located at 301 Binney Street, Cambridge, Massachusetts, where we occupy approximately 71,562 square feet of research and development, laboratory and office space. This lease expires in 2029. We believe that our office and laboratory space is sufficient to meet our needs for the foreseeable future and that suitable additional space will be available as and when needed.

**ITEM 3. LEGAL PROCEEDINGS**

From time to time, we may be subject to legal proceedings and claims in the ordinary course of business. We are not currently aware of any such proceedings or claims that we believe will have, individually or in the aggregate, a material adverse effect on our business, financial condition or results of operations.

**ITEM 4. MINE SAFETY DISCLOSURES**

Not applicable.

## PART II

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

#### Certain Information Regarding the Trading of Our Common Stock

Our common stock trades under the symbol "GBIO" on the Nasdaq Global Select Market and has been publicly traded since June 16, 2020. Prior to this time, there was no public market for our common stock.

#### Holder of Our Common Stock

As of February 28, 2021, there were approximately 54 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

#### Dividends

We have never declared or paid cash dividends on our common stock since our inception. We currently intend to retain all available funds and any future earnings to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to declare and pay dividends will be made at the discretion of our board of directors and will depend on then-existing conditions, including our results of operations, financial condition, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

#### Use of Proceeds from the Initial Public Offering

In June 2020, we closed our initial public offering, or IPO, of our common stock, pursuant to which we issued and sold 12,105,263 shares of our common stock, including 1,578,947 shares sold by us pursuant to the full exercise of the underwriters' option to purchase additional shares, at a price to the public of \$19.00 per share for aggregate gross proceeds of \$230.0 million.

All of the shares issued and sold in the IPO were registered under the Securities Act pursuant to a Registration Statement on Form S-1 (File No. 333-238608), which was declared effective by the SEC on June 11, 2020. J.P. Morgan Securities LLC, Jefferies LLC and Cowen and Company, LLC acted as joint book-running managers and Wedbush PacGrow acted as lead manager of our IPO.

We received aggregate net proceeds of approximately \$210.7 million after deducting underwriting discounts and commissions and other offering expenses payable by us. None of the underwriting discounts and commissions or offering expenses were incurred or paid to directors or officers of ours or their associates or to persons owning 10 percent or more of our common stock or to any of our affiliates.

As of December 31, 2020, we have used approximately \$40.2 million of net offering proceeds. There has been no material change in our planned use of the net proceeds from the offering as described in our final prospectus filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC on June 12, 2020.

#### Recent Sales of Unregistered Securities

Set forth below is information regarding shares of our common stock and preferred stock issued and stock options granted by us during the year ended December 31, 2020 that were not registered under the Securities Act. Also included is the consideration, if any, received by us for such shares, warrants and options and information relating to the section of the Securities Act, or rule of the SEC, under which exemption from registration was claimed.

##### *(a) Issuances of Convertible Preferred Stock*

On January 9, 2020, we issued and sold 19,936,296 shares of our Series C preferred stock to 54 investors at a price per share of \$5.5914 in cash, for an aggregate purchase price of \$111.5 million.

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No underwriters were involved in the foregoing issuance of securities. The securities described in this section (a) were issued to investors in reliance upon the exemption from the registration requirements of the Securities Act, as set forth in Section 4(a)(2) under the Securities Act and, in certain cases, Regulation D thereunder, relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration statement or an available exemption from such registration.

Upon the closing of our IPO in June 2020, all outstanding shares of our convertible preferred stock automatically converted into 27,094,085 shares of common stock.

### **(b) Stock Option Grants and Exercises**

Between January 1, 2020 and June 11, 2020, we granted options to our employees, advisors and consultants to purchase an aggregate of 2,340,596 shares of common stock, with exercise prices ranging from \$5.16 to \$19.00 per share, pursuant to our 2017 Stock Incentive Plan. During the year ended December 31, 2020, we issued 788,791 shares of our common stock upon the exercise of stock options outstanding under our 2017 Stock Incentive Plan for aggregate consideration of \$3.5 million.

No underwriters were involved in the foregoing issuance of securities. The stock options and shares of common stock issued upon the exercise of the options were issued pursuant to written compensatory plans or arrangements with our employees, in reliance on the exemption provided by Rule 701 promulgated under the Securities Act, or pursuant to Section 4(2) of the Securities Act, relative to transactions by an issuer not involving any public offering, to the extent an exemption from such registration was required. All recipients either received adequate information about our company or had access, through employment and other relationships, to such information. On June 12, 2020, we filed a registration statement on Form S-8 under the Securities Act to register all of the shares of our common stock subject to outstanding options.

## **ITEM 6. SELECTED FINANCIAL DATA**

We are a smaller reporting company, as defined in Rule 12b-2 under the Exchange Act, for this reporting period and are not required to provide the information required under this item.

## **ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS**

*The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes appearing at the end of this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report, our actual results could differ materially from the results described in, or implied by, the forward-looking statements contained in the following discussion and analysis.*

### **Overview**

We are an innovative genetic medicines company creating a new class of gene therapy utilizing our proprietary non-viral gene therapy platform to provide durable, redosable treatments for millions of patients living with rare and prevalent diseases. Our non-viral gene therapy platform incorporates our high-capacity DNA construct called closed-ended DNA, or ceDNA; our cell-targeted lipid nanoparticle delivery system, or ctLNP; and our established, scalable capsid-free manufacturing process. Using our approach, we are developing novel gene therapies to provide targeted delivery of genetic payloads that include large and multiple genes to a range of tissues across a broad array of diseases. We are also engineering our gene therapies to be redosable, which may

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enable individualized patient titration to reach the desired level of therapeutic expression and to maintain efficacy throughout a patient's life.

Since our inception in October 2016, we have focused substantially all of our resources on building our non-viral gene therapy platform, establishing and protecting our intellectual property portfolio, conducting research and development activities, developing our manufacturing process, organizing and staffing our company, business planning, raising capital and providing general and administrative support for these operations. We do not have any products approved for sale and have not generated any revenue from product sales. To date, we have funded our operations with proceeds from instruments convertible into convertible preferred stock (which converted into convertible preferred stock in 2017) and the sales of convertible preferred stock (which converted into common stock in 2020) and, most recently, with proceeds from the sale of common stock in our public offerings. In June 2020, we completed our initial public offering, or IPO, pursuant to which we issued and sold 12,105,263 shares of our common stock, including 1,578,947 shares sold by us pursuant to the full exercise of the underwriters' option to purchase additional shares. We received net proceeds of \$210.7 million, after deducting underwriting discounts and commissions and other offering expenses. In January 2021, we issued and sold 9,200,000 shares of our common stock, including 1,200,000 shares sold by us pursuant to the full exercise of the underwriters' option to purchase additional shares, in a follow-on public offering, resulting in net proceeds of \$211.3 million after deducting underwriting discounts and commissions and other offering expenses.

Since our inception, we have incurred significant operating losses. Our ability to generate any product revenue or product revenue sufficient to achieve profitability will depend on the successful development and eventual commercialization of one or more product candidates we may develop. For the years ended December 31, 2020 and 2019, we reported net losses of \$80.5 million and \$61.3 million, respectively. As of December 31, 2020, we had an accumulated deficit of \$189.0 million. We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. We expect that our expenses and capital requirements will increase substantially in connection with our ongoing activities, particularly if and as we:

- continue our current research programs and conduct additional research programs;
- advance any product candidates we identify into preclinical and clinical development;
- expand the capabilities of our proprietary non-viral gene therapy platform;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- obtain, expand, maintain, defend and enforce our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel;
- ultimately establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- establish a commercial manufacturing source and secure supply chain capacity sufficient to provide commercial quantities of any product candidates for which we may obtain regulatory approval; and
- add operational, legal, compliance, financial and management information systems and personnel to support our research, product development, future commercialization efforts and operations as a public company.

We will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for any product candidates we may develop. If we obtain regulatory approval for any product candidates we may develop, we expect to incur significant expenses related to developing our commercial capability to support product sales, marketing and distribution. Further, we expect to continue to incur additional costs associated with operating as a public company.

As a result, 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 through a combination of equity offerings, debt financings, collaborations, strategic alliances and/or licensing arrangements. We may be unable to raise additional funds or enter into such other

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agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements when needed or on terms acceptable to us, we would be required to delay, limit, reduce or terminate our product development or future commercialization of one or more of our product candidates.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve 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, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe that our existing cash, cash equivalents and marketable securities, including the net proceeds from the offering we completed in January 2021, will enable us to fund our operating expenses and capital expenditures into 2024. We have based our estimates as to how long we expect we will be able to fund our operations on assumptions that may prove to be wrong. We could use our available capital resources sooner than we currently expect, in which case we would be required to obtain additional financing, which may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. See “—Liquidity and capital resources.”

### **COVID-19**

In March 2020, COVID-19 was declared a global pandemic by the World Health Organization and to date, the COVID-19 pandemic continues to present a substantial public health and economic challenge around the world. The length of time and full extent to which the COVID-19 pandemic may directly or indirectly impact our business, results of operations and financial condition will depend on future developments that are highly uncertain, subject to change and difficult to predict. We, our contract development and manufacturing organizations, or CDMOs, and our contract research organizations, or CROs, experienced temporary reductions in the capacity to undertake research-scale production and to execute some preclinical studies. While these operations have since normalized, we, together with our CDMOs and CROs, are closely monitoring the impact of the COVID-19 pandemic on these operations.

We also plan to continue to closely monitor the ongoing impact of the COVID-19 pandemic on our employees and our other business operations. In an effort to provide a safe work environment for our employees, we have, among other things, limited employees in our office and lab facilities to those where on-site presence is needed for their job activities, increased the cadence of sanitization of our office and lab facilities, implemented various social distancing measures in our offices and labs including replacing all in-person meetings with virtual interactions, and are providing personal protective equipment for our employees present in our office and lab facilities. We are continuing to monitor the impact and effects of the COVID-19 pandemic and our response to it, and we expect to continue to take actions as may be required or recommended by government authorities or as we determine are in the best interests of our employees and other business partners in light of the pandemic.

### **Components of Our Results of Operations**

#### ***Operating expenses***

##### *Research and development expenses*

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts, and the development of our programs, which include:

- personnel-related costs, including salaries, benefits and stock-based compensation expense, for employees engaged in research and development functions;
- expenses incurred in connection with our research programs, including under agreements with third parties, such as consultants and contractors and CROs;
- the cost of developing and scaling our manufacturing process and manufacturing drug substance and drug product for use in our research and preclinical studies, including under agreements with third parties, such as consultants and contractors and CDMOs;



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- laboratory supplies and research materials;
- facilities, depreciation and amortization and other expenses, which include direct and allocated expenses for rent and maintenance of facilities and insurance; and
- payments made under third-party licensing agreements.

We expense research and development costs as incurred. Advance payments that we make for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

Our external research and development expenses consist of costs that include fees and other costs paid to consultants, contractors, CDMOs and CROs in connection with our preclinical and manufacturing activities. We do not allocate our research and development costs to specific programs because costs are deployed across multiple programs and our platform and, as such, are not separately classified. We expect that our research and development expenses will increase substantially as we advance our programs into clinical development and expand our discovery, research and preclinical activities in the near term and in the future. At this time, we cannot accurately estimate or know the nature, timing and costs of the efforts that will be necessary to complete the preclinical and clinical development of any product candidates we may develop. The successful development of any of our product candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development, including the following:

- the timing and progress of preclinical studies, including investigational new drug, or IND, -enabling studies;
- the number and scope of preclinical and clinical programs we decide to pursue;
- raising additional funds necessary to complete preclinical and clinical development of our product candidates;
- the timing of filing and acceptance of IND applications or comparable foreign applications that allow commencement of future clinical trials for our product candidates;
- the successful initiation, enrollment and completion of clinical trials, including under current good clinical practices;
- our ability to achieve positive results from our future clinical programs that support a finding of safety and effectiveness and an acceptable risk-benefit profile in the intended patient populations of any product candidates we may develop;
- the availability of specialty raw materials for use in production of our product candidates;
- our ability to establish arrangements with third-party manufacturers for clinical supply;
- our ability to establish new licensing or collaboration arrangements;
- the receipt and related terms of regulatory approvals from the FDA, and other applicable regulatory authorities;
- our ability to establish, obtain, maintain, enforce and defend patent, trademark, trade secret protection and other intellectual property rights or regulatory exclusivity for any product candidates we may develop and our technology; and
- our ability to maintain a continued acceptable safety, tolerability and efficacy profile of our product candidates following approval.

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

### *General and administrative expenses*

General and administrative expenses consist primarily of personnel-related costs, including salaries, benefits and stock-based compensation, for employees engaged in executive, legal, finance and accounting and other

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administrative functions. General and administrative expenses also include professional fees for legal, patent, consulting, investor and public relations and accounting and audit services as well as direct and allocated facility-related costs.

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 programs and platform. We also anticipate that we will continue to incur increased accounting, audit, legal, regulatory, compliance, director and officer insurance costs and investor and public relations expenses associated with operating as a public company.

### **Other income (expense)**

#### *Interest income and other income (expense), net*

Interest income consists of interest earned on our invested cash balances. Other income (expense) consists of miscellaneous income and expense unrelated to our core operations.

### **Income taxes**

Since our inception, we have not recorded any income tax benefits for the net losses we have incurred or for the research and development tax credits earned in each year, as we believe, based upon the weight of available evidence, that it is more likely than not that all of our net operating loss carryforwards and tax credit carryforwards will not be realized.

As of December 31, 2020, we had federal net operating loss carryforwards of \$177.3 million, which may be available to offset future taxable income, of which \$8.2 million of the total net operating loss carryforwards begin to expire in 2036, while the remaining \$169.1 million do not expire but may be limited in their usage to an annual deduction equal to 80% of annual taxable income. In addition, as of December 31, 2020, we had state net operating loss carryforwards of \$174.7 million, which may be available to offset future taxable income and expire at various dates beginning in 2036. As of December 31, 2020, we also had federal and state research and development tax credit carryforwards of \$6.3 million and \$3.9 million, respectively, which may be available to reduce future tax liabilities and expire at various dates beginning in 2036 and 2032, respectively. Due to our history of cumulative net losses since inception and uncertainties surrounding our ability to generate future taxable income, we have recorded a full valuation allowance against our net deferred tax assets at each balance sheet date.

## **Results of Operations**

### **Comparison of the Years Ended December 31, 2020 and 2019**

The following table summarizes our results of operations for the years ended December 31, 2020 and 2019:

	<b>Year Ended December 31,</b>		<b>Change</b>
	<b>2020</b>	<b>2019</b>	
	<b>(in thousands)</b>		
Operating expenses:			
Research and development	\$ 58,532	\$ 50,134	\$ 8,398
General and administrative	22,582	12,168	10,414
Total operating expenses	<u>81,114</u>	<u>62,302</u>	<u>18,812</u>
Loss from operations	(81,114)	(62,302)	(18,812)
Other income (expense):			
Interest income and other income (expense), net	591	985	(394)
Net loss	<u>\$ (80,523)</u>	<u>\$ (61,317)</u>	<u>\$ (19,206)</u>

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### *Research and Development Expenses*

	<u>Year Ended December 31,</u>		<u>Change</u>
	<u>2020</u>	<u>2019</u> (in thousands)	
Personnel-related	\$17,461	\$ 12,847	\$4,614
Stock-based compensation	4,301	2,753	1,548
Preclinical and manufacturing	16,849	15,027	1,822
Facilities	9,394	9,553	(159)
Lab supplies	4,002	4,124	(122)
Consulting and professional services	3,031	2,629	402
Other	3,494	3,201	293
Total research and development expenses	<u>\$58,532</u>	<u>\$ 50,134</u>	<u>\$8,398</u>

Research and development expenses were \$58.5 million for the year ended December 31, 2020 compared to \$50.1 million for the year ended December 31, 2019. The increases in personnel-related costs and stock-based compensation costs of \$4.6 million and \$1.5 million, respectively, were primarily due to increased headcount in our research and development function. The increase in preclinical and manufacturing costs of \$1.8 million was primarily due to increased preclinical spend as we prepare to advance our two lead programs into IND-enabling studies. The increase in consulting and professional services of \$0.4 million was primarily due to consulting services to develop and scale our manufacturing process.

### *General and Administrative Expenses*

	<u>Year Ended December 31,</u>		<u>Change</u>
	<u>2020</u>	<u>2019</u> (in thousands)	
Personnel related	\$ 8,927	\$ 4,279	\$ 4,648
Stock-based compensation	4,111	1,454	2,657
Professional and consultant fees	6,987	4,465	2,522
Facilities	1,576	1,217	359
Other	981	753	228
Total general and administrative expenses	<u>\$ 22,582</u>	<u>\$ 12,168</u>	<u>\$10,414</u>

General and administrative expenses were \$22.6 million for the year ended December 31, 2020, compared to \$12.2 million for the year ended December 31, 2019. The increases in personnel-related costs and stock-based compensation costs of \$4.6 million and \$2.7 million, respectively, were primarily a result of an increase in headcount in our general and administrative function. Professional and consultant fees increased by \$2.5 million primarily due to professional fees relating to accounting, audit and legal services as well as costs associated with ongoing business activities and operating as a public company.

### *Other Income (Expense)*

Interest income and other income (expense), net for the year ended December 31, 2020 was \$0.6 million compared to \$1.0 million for the year ended December 31, 2019 and consisted primarily of interest income earned on invested cash balances. The decrease in interest income from 2019 was primarily due to lower interest rates during 2020.

### **Liquidity and Capital Resources**

Since our inception, we have incurred significant operating losses. We expect to incur significant expenses and operating losses for the foreseeable future as we support our continued research activities and development of our

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programs and platform. We have not yet commercialized any product candidates and we do not expect to generate revenue from sales of any product candidates for several years, if at all. To date, we have funded our operations with proceeds from instruments convertible into convertible preferred stock (which converted into convertible preferred stock in 2017), the sale of convertible preferred stock and, most recently, with proceeds from the sale of common stock in our public offerings. As of December 31, 2020, we had cash, cash equivalents and marketable securities of \$262.3 million. In June 2020, we completed our IPO, pursuant to which we issued and sold 12,105,263 shares of our common stock, including 1,578,947 shares sold by us pursuant to the full exercise of the underwriters' option to purchase additional shares. We received net proceeds of \$210.7 million, after deducting underwriting discounts and commissions and other expenses. In January 2021, we issued and sold 9,200,000 shares of our common stock, including 1,200,000 shares sold by us pursuant to the full exercise of the underwriters' option to purchase additional shares, in a follow-on public offering, resulting in net proceeds of \$211.3 million after deducting underwriting discounts and commissions and other offering expenses.

### **Cash Flows**

The following table summarizes our sources and uses of cash for each of the periods presented:

	Year Ended December 31,	
	2020	2019
	(in thousands)	
Cash used in operating activities	\$ (70,142)	\$(40,346)
Cash provided by (used in) investing activities	(205,196)	47,985
Cash provided by financing activities	323,095	78
Net increase in cash, cash equivalents and restricted cash	<u>\$ 47,757</u>	<u>\$ 7,717</u>

#### *Operating activities*

During the year ended December 31, 2020, operating activities used \$70.1 million of cash, primarily resulting from our net loss of \$80.5 million and changes in our operating assets and liabilities of \$1.7 million, both partially offset by non-cash charges of \$12.1 million. Net cash used by changes in our operating assets and liabilities for the year ended December 31, 2020 consisted primarily of a \$2.8 million increase in prepaid expenses and other current assets and a \$1.1 million decrease in deferred rent, partially offset by an increase of \$2.0 million in accounts payable and accrued expenses and other current liabilities and a decrease of \$0.4 million in tenant receivable.

During the year ended December 31, 2019, operating activities used \$40.3 million of cash, primarily resulting from our net loss of \$61.3 million, partially offset by net non-cash charges of \$5.7 million and net cash provided by changes in our operating assets and liabilities of \$15.2 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2019 consisted primarily of a \$13.0 million increase in deferred rent and a \$3.2 million increase in accounts payable and accrued expenses and other current liabilities, partially offset by a \$1.9 million increase in prepaid expenses and other current assets.

Changes in accounts payable, accrued expenses and other current liabilities and prepaid expenses and other current assets in all periods were generally due to growth in our business, the advancement of our research programs and the timing of vendor invoicing and payments. Changes in deferred rent were primarily related to a tenant improvement allowance from our landlord.

#### *Investing Activities*

During the year ended December 31, 2020, net cash used in investing activities was \$205.2 million, due to the purchases of marketable securities and property and equipment during the period, partially offset by sales and maturities of marketable securities. Property and equipment purchases of \$5.5 million were primarily related to leasehold improvements and lab equipment for our facility in Cambridge, Massachusetts.

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During the year ended December 31, 2019, net cash provided by investing activities was \$48.0 million, due primarily to net sales and maturities of marketable securities, partially offset by the acquisition of property and equipment during the year. Property and equipment purchases during the year ended December 31, 2019 primarily related to leasehold improvements and lab equipment for our new facility in Cambridge, Massachusetts.

### *Financing Activities*

During the year ended December 31, 2020, net cash provided by financing activities was \$323.1 million, consisting primarily of proceeds from our IPO of common stock of \$213.9 million, net of discounts and commissions, and proceeds from the sale of our Series C preferred stock of \$108.9 million, partially offset by the payment of \$3.2 million of public offering costs. We also received proceeds of \$3.6 million from the exercise of common stock options.

During the year ended December 31, 2019, net cash provided by financing activities was \$0.1 million, consisting primarily of proceeds from the exercise of common stock options.

### *Funding Requirements*

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and initiate clinical trials for our product candidates in development. The timing and amount of our operating expenditures will depend largely on:

- the identification of additional research programs and product candidates;
- the scope, progress, costs and results of preclinical and clinical development for any product candidates we may develop;
- the costs, timing and outcome of regulatory review of any product candidates we may develop;
- the cost and timing of completion of commercial-scale manufacturing activities;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any product candidates we may develop for which we receive marketing approval;
- the costs and scope of the continued development of our non-viral gene therapy platform;
- the costs of satisfying any post-marketing requirements;
- the revenue, if any, received from commercial sales of product candidates we may develop for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting applications for patents, obtaining, maintaining, defending and enforcing our intellectual property rights and defending against any intellectual property-related claims, including claims of infringement, misappropriation or other violation of third-party intellectual property;
- the costs of operational, financial and management information systems and associated personnel;
- the associated costs in connection with any acquisition of in-licensed products, intellectual property and technologies; and
- the costs of operating as a public company.

We believe that our existing cash, cash equivalents and marketable securities, including the net proceeds from the offering we completed in January 2021, will enable us to fund our operating expenses and capital expenditures into 2024. We have based our estimates as to how long we expect we will be able to fund our operations on assumptions that may prove to be wrong. We could use our available capital resources sooner than we currently expect, in which case we would be required to obtain additional financing, which may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our

financial condition and our ability to pursue our business strategy. We do not have any committed external source of funds. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources. If we raise additional funds by issuing equity securities, our stockholders may experience dilution. Any future debt financing into which we enter would result in fixed payment obligations and may involve agreements that include grants of security interests on our assets and restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, granting liens over our assets, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. Any debt financing or additional equity that we raise may contain terms that could adversely affect the holdings or the rights of our common stockholders.

If we are unable to raise sufficient capital as and when needed, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidate we may develop, or be unable to expand our operations or otherwise capitalize on our business opportunities. If we raise additional funds through collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to future revenue streams or product candidates or grant licenses on terms that may not be favorable to us.

See “Risk Factors” for additional risks associated with our substantial capital requirements.

### **Critical accounting policies and significant judgments and estimates**

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States, or GAAP. 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, costs and expenses and the disclosure of contingent assets and liabilities in our consolidated 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 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 certain accrued research and development expenses. This process involves 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. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of the estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include those related to fees paid to:

- vendors in connection with discovery and preclinical development activities;
- CROs in connection with preclinical studies and testing; and
- CDMOs in connection with the process development and scale up activities and the production of materials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CROs and CDMOs that conduct

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services and supply materials. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. 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 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. While the majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; some require advance payments. 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. We record these as prepaid expenses on our consolidated balance sheet.

### ***Stock-based compensation***

We measure all stock-based awards granted to employees, non-employees and directors based on their fair value on the date of the grant using the Black-Scholes option-pricing model for options or the difference between the purchase price, if any, and the fair value of our common stock for restricted stock awards and units. Compensation expense for awards with service-based vesting is generally recognized over the vesting period of the award using the straight-line method to record the expense. We use the graded-vesting method to record the expense of awards with both service-based and performance-based vesting conditions, commencing once achievement of the performance condition becomes probable. We account for forfeitures of share-based awards as they occur.

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

We determine the fair market value of our common stock using the closing price of our common stock as reported on the Nasdaq Global Select Market.

### **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 SEC.

### **Recently Issued and Adopted 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 to our consolidated financial statements included in this Annual Report.

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

We are a smaller reporting company, as defined in Rule 12b-2 under the Exchange Act, for this reporting period and are not required to provide the information required under this item.

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**ITEM 8. CONSOLIDATED FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA**

**GENERATION BIO CO.**

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## Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Generation Bio Co.

### Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Generation Bio Co. (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the two years in the period ended December 31, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2020, in conformity with U.S. generally accepted accounting principles.

### Basis for Opinion

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

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

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2018.

Boston, Massachusetts  
March 18, 2021

**Generation Bio Co.**  
**Consolidated Balance Sheets**  
(In thousands, except share and per share amounts)

	December 31,	
	2020	2019
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 62,889	\$ 15,076
Marketable securities	199,438	—
Tenant receivable	—	448
Prepaid expenses and other current assets	5,408	2,577
Restricted cash	—	55
Total current assets	267,735	18,156
Property and equipment, net	23,781	21,845
Restricted cash, noncurrent	2,051	2,052
Deferred offering costs	336	87
Other long-term assets	252	—
Total assets	<u>\$ 294,155</u>	<u>\$ 42,140</u>
<b>Liabilities, Convertible Preferred Stock and Stockholders' Equity (Deficit)</b>		
Current liabilities:		
Accounts payable	\$ 267	\$ 2,251
Accrued expenses and other current liabilities	10,953	6,907
Total current liabilities	11,220	9,158
Deferred rent, net of current portion	14,922	15,981
Total liabilities	26,142	25,139
Commitments and contingencies (Note 11)		
Convertible preferred stock (Series A, B and C), \$0.0001 par value; no shares and 26,425,664 shares authorized at December 31, 2020 and 2019, respectively; no shares and 26,425,664 shares issued and outstanding at December 31, 2020 and 2019, respectively		
	—	115,593
Stockholders' equity (deficit):		
Preferred stock, \$0.0001 par value; 5,000,000 and no shares authorized at December 31, 2020 and 2019, respectively; no shares issued or outstanding	—	—
Common stock, \$0.0001 par value; 150,000,000 and 46,750,000 shares authorized at December 31, 2020 and 2019, respectively; 46,970,012 and 6,976,077 shares issued at December 31, 2020 and 2019, respectively; 46,291,877 and 5,270,889 shares outstanding at December 31, 2020 and 2019, respectively	5	1
Additional paid-in capital	456,974	9,859
Accumulated other comprehensive income	9	—
Accumulated deficit	(188,975)	(108,452)
Total stockholders' equity (deficit)	268,013	(98,592)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	<u>\$ 294,155</u>	<u>\$ 42,140</u>

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

**Generation Bio Co.**  
**Consolidated Statements of Operations and Comprehensive Loss**  
**(In thousands, except share and per share amounts)**

	<b>Year Ended December 31,</b>	
	<b>2020</b>	<b>2019</b>
Operating expenses:		
Research and development	\$ 58,532	\$ 50,134
General and administrative	22,582	12,168
Total operating expenses	<u>81,114</u>	<u>62,302</u>
Loss from operations	(81,114)	(62,302)
Other income (expense):		
Interest income and other income (expense), net	591	985
Net loss and net loss attributable to common stockholders	<u>\$ (80,523)</u>	<u>\$ (61,317)</u>
Net loss per share attributable to common stockholders, basic and diluted	<u>\$ (2.95)</u>	<u>\$ (12.96)</u>
Weighted average common shares outstanding, basic and diluted	<u>27,256,494</u>	<u>4,731,519</u>
Comprehensive loss:		
Net loss	\$ (80,523)	\$ (61,317)
Other comprehensive income:		
Unrealized gains on marketable securities	9	9
Comprehensive loss	<u>\$ (80,514)</u>	<u>\$ (61,308)</u>

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

**Generation Bio Co.**  
**Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)**  
(In thousands, except share amounts)

	Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
<b>Balances at December 31, 2018</b>	26,425,664	\$ 115,593	4,054,475	\$ 1	\$ 5,552	\$ (9)	\$ (47,135)	\$ (41,591)
Issuance of common stock for license	—	—	125,677	—	—	—	—	—
Issuance of common stock upon exercise of stock options	—	—	34,740	—	100	—	—	100
Vesting of restricted common stock	—	—	1,055,997	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	4,207	—	—	4,207
Unrealized gains on marketable securities	—	—	—	—	—	9	—	9
Net loss	—	—	—	—	—	—	(61,317)	(61,317)
<b>Balances at December 31, 2019</b>	<u>26,425,664</u>	<u>\$ 115,593</u>	<u>5,270,889</u>	<u>\$ 1</u>	<u>\$ 9,859</u>	<u>\$ —</u>	<u>\$ (108,452)</u>	<u>\$ (98,592)</u>
Issuance of Series C convertible preferred stock, net of issuance costs of \$2,640	19,936,296	108,832	—	—	—	—	—	—
Conversion of convertible preferred stock into common stock upon initial public offering	(46,361,960)	(224,425)	27,094,085	3	224,422	—	—	224,425
Issuance of common stock upon initial public offering, net of issuance costs of \$3,185	—	—	12,105,263	1	210,714	—	—	210,715
Issuance of common stock upon exercise of stock options	—	—	792,845	—	3,567	—	—	3,567
Vesting of restricted common stock	—	—	1,022,234	—	—	—	—	—
Vesting of restricted common stock units	—	—	6,561	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	8,412	—	—	8,412
Unrealized gains on marketable securities	—	—	—	—	—	9	—	9
Net loss	—	—	—	—	—	—	(80,523)	(80,523)
<b>Balances at December 31, 2020</b>	<u>—</u>	<u>\$ —</u>	<u>46,291,877</u>	<u>\$ 5</u>	<u>\$ 456,974</u>	<u>\$ 9</u>	<u>\$ (188,975)</u>	<u>\$ 268,013</u>

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

**Generation Bio Co.**  
**Consolidated Statements of Cash Flows**  
(In thousands)

	<b>Year Ended December 31,</b>	
	<b>2020</b>	<b>2019</b>
<b>Cash flows from operating activities:</b>		
Net loss	\$ (80,523)	\$ (61,317)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	8,412	4,207
Depreciation and amortization expense	3,432	1,864
Amortization (accretion) of premium (discount) on marketable securities, net	249	(317)
Gain on sale of property and equipment	—	(10)
Changes in operating assets and liabilities:		
Tenant receivable	448	840
Prepaid expenses and other current assets	(2,831)	(1,863)
Other noncurrent assets	(252)	—
Accounts payable	(1,444)	761
Accrued expenses and other current liabilities	3,426	2,470
Deferred rent	(1,059)	13,019
Net cash used in operating activities	<u>(70,142)</u>	<u>(40,346)</u>
<b>Cash flows from investing activities:</b>		
Purchases of property and equipment	(5,518)	(19,986)
Proceeds from sale of property and equipment	—	80
Purchases of marketable securities	(243,178)	(20,789)
Sales and maturities of marketable securities	43,500	88,680
Net cash provided by (used in) investing activities	<u>(205,196)</u>	<u>47,985</u>
<b>Cash flows from financing activities:</b>		
Proceeds from issuance of convertible preferred stock, net of issuance costs incurred and paid in current period	108,854	—
Proceeds from initial public offering of common stock, net of underwriting discounts and commissions	213,900	—
Proceeds from exercise of stock options	3,567	100
Payment of deferred offering cost	(41)	(22)
Payment of initial public offering costs	(3,185)	—
Net cash provided by financing activities	<u>323,095</u>	<u>78</u>
<b>Net increase in cash, cash equivalents and restricted cash</b>	<b>47,757</b>	<b>7,717</b>
Cash, cash equivalents and restricted cash at beginning of period	17,183	9,466
Cash, cash equivalents and restricted cash at end of period	<u>\$ 64,940</u>	<u>\$ 17,183</u>
<b>Supplemental disclosure of noncash investing and financing information:</b>		
Conversion of convertible preferred stock to common stock	\$ 224,425	\$ —
Purchases of property and equipment included in accounts payable and accrued expenses	\$ 494	\$ 644
Issuance costs included in accrued expenses	\$ 295	\$ 65

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

**Generation Bio Co.**  
**Notes to Condensed Consolidated Financial Statements**

**1. Nature of the Business and Basis of Presentation**

The Company was incorporated on October 21, 2016 as Torus Therapeutics, Inc. and subsequently changed its name to Generation Bio Co. (the “Company”). The Company is an innovative genetic medicines company creating a new class of gene therapy utilizing its proprietary non-viral gene therapy platform to provide durable, redosable treatments for millions of patients living with rare and prevalent diseases. The Company’s non-viral gene therapy platform incorporates its high-capacity DNA construct called closed-ended DNA (“ceDNA”), its cell-targeted lipid nanoparticle delivery system (“ctLNP”) and its established, scalable capsid-free manufacturing process. Using its approach, the Company is developing novel gene therapies to provide targeted delivery of genetic payloads that include large and multiple genes to a range of tissues across a broad array of diseases. The Company is also engineering its gene therapies to be redosable, which may enable individualized patient titration to reach the desired therapeutic expression and to maintain efficacy throughout a patient’s life. The Company is headquartered in Cambridge, Massachusetts.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations, the ability to establish clinical- and commercial-scale manufacturing processes and the ability to secure additional capital to fund operations. Programs currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization of a product. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company’s development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

In June 2020, the Company completed its initial public offering (“IPO”) pursuant to which it issued and sold 12,105,263 shares of its common stock, including 1,578,947 shares pursuant to the full exercise of the underwriters’ option to purchase additional shares, at a public offering price of \$19.00 per share, resulting in net proceeds of \$210.7 million, after deducting underwriting discounts and commissions and other offering expenses. Upon the closing of the IPO, all of the Company’s outstanding convertible preferred stock automatically converted into shares of common stock. In January 2021, the Company issued and sold 9,200,000 shares of our common stock, including 1,200,000 shares pursuant to the full exercise of the underwriters’ option to purchase additional shares, in a follow-on public offering, resulting in net proceeds of \$211.3 million after deducting underwriting discounts and commissions and other offering expenses.

The accompanying consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Since inception, the Company has funded its operations with proceeds from the sales of instruments convertible into convertible preferred stock (which converted into convertible preferred stock in 2017), the sale of convertible preferred stock, and most recently, with proceeds from the sale of common stock in underwritten public offerings. The Company has incurred recurring losses, including net losses of \$80.5 million for the year ended December 31, 2020. As of December 31, 2020, the Company had an accumulated deficit of \$189.0 million. The Company expects to continue to generate operating losses in the foreseeable future. As of March 18, 2021, the issuance date of these consolidated financial statements, the Company expects that its cash, cash equivalents and marketable securities will be sufficient to fund its operating expenses and capital expenditure requirements for at least 12 months.

The Company will need to obtain additional funding through public or private equity offerings, debt financings, collaborations, strategic alliances and/or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and the Company may not be able to enter into collaborative or strategic alliances or licensing arrangements. The terms of any financing may adversely affect the holdings or the rights of

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the Company's stockholders. Arrangements with collaborators or others may require the Company to relinquish rights to certain of its technologies or programs. If the Company is unable to obtain funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs, pipeline expansion or commercialization efforts, which could adversely affect its business prospects. Although management will continue to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations when needed or at all.

The accompanying consolidated financial statements reflect the operations of the Company and the Company's wholly owned subsidiary, Generation Bio Securities Corporation. Intercompany balances and transactions have been eliminated in consolidation. The accompanying consolidated financial statements have been prepared in conformity with generally accepted accounting principles ("GAAP") in the United States of America. Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Update ("ASU") of the Financial Accounting Standards Board ("FASB").

## **2. Summary of Significant Accounting Policies**

### ***Use of estimates***

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual of research and development expenses and stock-based compensation expense. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates, as there are changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results may differ from those estimates or assumptions.

### ***Concentrations of credit risk and of significant suppliers***

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents, and marketable securities. The Company believes it is not exposed to significant credit risk due to the financial strength of the depository institutions in which the cash and cash equivalents are held. The Company maintains its cash equivalents in money market funds that invest in U.S. treasury securities. The Company's marketable securities as of December 31, 2020 consisted of U.S government treasury securities, commercial paper and corporate debt securities. The Company has adopted an investment policy that limits the amounts the Company may invest in the securities of single issuer with the exclusion of the U.S. government. The Company has not experienced any credit losses and does not believe that it is subject to significant credit risk.

The Company is dependent on a small number of third-party suppliers for its drug substance and drug product. In particular, the Company relies, and expects to continue to rely, on third-party suppliers for certain materials and components required for the production of any product candidates it may develop for its programs. These programs could be adversely affected by a significant interruption in the supply process.

### ***Cash equivalents***

The Company considers all highly liquid investments with a remaining maturity when purchased of three months or less to be cash equivalents.

### ***Restricted cash***

Amounts included in restricted cash represent amounts pledged as collateral for letters of credit required for security deposits on the Company's leased facilities. These amounts are classified as restricted cash (current and noncurrent) on the Company's consolidated balance sheets.

**Marketable securities**

The Company's marketable securities, which consisted of debt securities as of December 31, 2020, are classified as available-for-sale and are reported at fair value. Unrealized gains and losses on available-for-sale debt securities are reported as a component of accumulated other comprehensive income (loss) in stockholders' equity (deficit). Realized gains and losses and declines in value determined to be other than temporary are based on the specific identification method and are included as a component of other income (expense), net in the consolidated statements of operations and comprehensive loss.

The Company evaluates its marketable securities with unrealized losses for other-than-temporary impairment. When assessing marketable securities for other-than-temporary declines in value, the Company considers such factors as, among other things, how significant the decline in value is as a percentage of the original cost, how long the market value of the investment has been less than its original cost, the Company's ability and intent to retain the investment for a period of time sufficient to allow for any anticipated recovery in fair value and market conditions in general. If any adjustment to fair value reflects a decline in the value of the investment that the Company considers to be "other than temporary," the Company reduces the investment to fair value through a charge to the statement of operations and comprehensive loss. No such adjustments were necessary during the periods presented.

**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 financial liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

The Company's cash equivalents and marketable securities are carried at fair value, determined according to the fair value hierarchy described above (see Note 3). The carrying values of the Company's accounts payable and accrued expenses approximate their fair values due to the short-term nature of these liabilities.

**Deferred rent**

Payment escalations, rent holidays and other lease incentives that may be included in lease agreements are accrued or deferred as appropriate such that rent expense for each lease is recognized on a straight-line basis over the respective lease term. Adjustments for such items are recorded as deferred rent and amortized over the respective lease terms.

**Property and equipment**

Property and equipment are stated at cost less accumulated depreciation and amortization. Depreciation and amortization expense is recognized using the straight-line method over the estimated useful life of each asset as follows:

	Estimated Useful Life
Laboratory equipment	5 years



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	Estimated Useful Life
Computer equipment and software	3 years
Furniture and fixtures	5 years
Leasehold improvements	Shorter of remaining life of lease or useful life

Costs for capital assets not yet placed into service are capitalized as construction-in-progress and depreciated once placed into service. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation and amortization are removed from the accounts and any resulting gain or loss is included in loss from operations. Expenditures for repairs and maintenance which do not improve or extend the life of the respective assets are charged to expense as incurred.

### ***Impairment of long-lived assets***

Long-lived assets consist of property and equipment. The Company evaluates the recoverability of its long-lived assets when circumstances indicate that an event of impairment may have occurred. The Company recognizes an impairment loss only if the carrying amount of a long-lived asset is not recoverable based on its undiscounted future cash flows. Impairment is measured based on the difference between the carrying value of the related assets and the fair value of such assets. The Company did not record any impairment losses on long-lived assets during the years ended December 31, 2020 or 2019.

### ***Classification and accretion of convertible preferred stock***

The Company's convertible preferred stock outstanding prior to the IPO was classified outside of stockholders' equity (deficit) on the consolidated balance sheets because the holders of such shares had redemption rights in the event of a deemed liquidation that, in certain situations, was not solely within the control of the Company and would have required the redemption of the then-outstanding convertible preferred stock.

### ***Segment information***

The Company has determined that its chief executive officer is the chief operating decision maker ("CODM"). The CODM reviews financial information presented on a consolidated basis. Resource allocation decisions are made by the CODM based on consolidated results. There are no segment managers who are held accountable by the CODM for operations, operating results, and planning for levels or components below the consolidated unit level. As such, the Company has concluded that it operates as one segment. All long-lived assets are located in the United States.

### ***Research and development costs***

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries and bonuses, stock-based compensation, employee benefits, facilities costs, laboratory supplies, depreciation and amortization, manufacturing expenses and external costs of vendors engaged to conduct preclinical development activities as well as the cost of licensing technology.

Upfront payments and milestone payments made for the licensing of technology with no alternative future use are expensed as research and development expenses in the period in which they are incurred. Advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed.

### ***Research and manufacturing contract costs and accruals***

The Company has entered into various research and development and manufacturing contracts. These agreements are generally cancelable, and costs for research and development and manufacturing activities are expensed in

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the period in which they are incurred. Payments for such activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred. The Company records accruals for costs incurred but not billed. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the research studies and manufacturing activities, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

### ***Patent costs***

All patent-related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses.

### ***Stock-based compensation***

The Company measures stock options with service-based vesting or performance-based vesting granted to employees, non-employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. The Company measures restricted common stock awards and units using the difference between the purchase price per share of the award or unit, if any, and the fair value of the Company's common stock at the date of grant.

Compensation expense for awards with service-based vesting is generally recognized over the vesting period of the award using the straight-line method to record the expense. The Company uses the graded-vesting method to record the expense of awards with both service-based and performance-based vesting conditions, commencing once achievement of the performance condition becomes probable. The Company accounts for forfeitures of share-based awards as they occur. 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 payroll costs are classified or in which the award recipient's service payments are classified.

### ***Comprehensive loss***

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. For the years ended December 31, 2020 and 2019, the Company's only element of other comprehensive loss was unrealized gains (losses) on available-for-sale debt securities.

### ***Income taxes***

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the 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 through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing

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authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. 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. The Company's policy is to recognize interest and/or penalties related to income tax matters in income tax expense. The Company had accrued no amounts for interest and penalties on its consolidated balance sheets at December 31, 2020 and 2019.

### ***Net loss per share***

Prior to closing of the IPO, the Company followed the two-class method when computing net income (loss) per share as the Company had issued shares that met the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income (loss) available to common stockholders for the period to be allocated between common stock and participating securities based upon their respective rights to share in the earnings as if all income (loss) for the period had been distributed.

Basic net income (loss) per share attributable to common stockholders is computed by dividing net income (loss) attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net income (loss) per share attributable to common stockholders is computed by adjusting net income (loss) attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to common stockholders is computed by dividing the diluted net income (loss) attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares.

The Company's participating securities contractually entitle the holders of such shares to participate in dividends but do not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

Subsequent to the closing of its IPO, the Company only has one class of shares outstanding and basic net income (loss) per common share is computed by dividing the net income (loss) by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) per common share is computed by dividing net income (loss) by the weighted average number of shares of common stock outstanding for the period, including potential dilutive common shares assuming the dilutive effect of outstanding stock awards. For periods in which the Company reports a net loss, diluted net loss per common share is the same as basic net loss per common share, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

The Company reported a net loss attributable to common stockholders for each of the years ended December 31, 2020 and 2019.

### ***Recently adopted accounting pronouncements***

In August 2018, the FASB issued ASU 2018-13, Fair Value Measurement (Topic 820): Disclosure Requirements for Fair Value Measurement. The new standard added, modified or removed disclosure requirements under Topic 820 for clarity and consistency. ASU 2018-13 is effective for all entities for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2019. The Company adopted ASU 2018-03 on January 1, 2020 and the adoption did not have a material impact on its consolidated financial statements.

***Recently issued accounting pronouncements***

From time to time, new accounting pronouncements are issued by the FASB or other standard setting bodies that the Company adopts as of the specified effective date. The Company qualifies as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012 and has elected not to “opt out” of the extended transition related to complying with new or revised accounting standards, which means that when a standard is issued or revised and it has different application dates for public and nonpublic companies, the Company can adopt the new or revised standard at the time nonpublic companies adopt the new or revised standard and can do so until such time that the Company either (i) irrevocably elects to “opt out” of such extended transition period or (ii) no longer qualifies as an emerging growth company.

In February 2016, the FASB issued ASU 2016-02, Leases (Topic 842). The new standard requires that all lessees recognize the assets and liabilities that arise from leases on the balance sheet and disclose qualitative and quantitative information about its leasing arrangements. In July 2018, the FASB issued ASU 2018-11, which provides entities with an additional transition method to adopt Topic 842. Under the new transition method, an entity initially applies the new lease requirements at the adoption date, not the earliest period presented, and recognizes a cumulative effect adjustment to the opening balance of retained earnings in the period of adoption. For public entities, the guidance was effective for annual reporting periods beginning after December 15, 2018 and for interim periods within those fiscal years. For nonpublic entities, the guidance was effective for annual reporting periods beginning after December 15, 2019. In November 2019, the FASB issued ASU 2019-10, which deferred the effective date for nonpublic entities to annual reporting periods beginning after December 15, 2020, and interim periods within fiscal years beginning after December 15, 2021. In June 2020, the FASB issued ASU 2020-05, which grants a one-year effective-date delay for nonpublic entities to annual reporting periods beginning after December 15, 2021 and to interim periods within fiscal years beginning after December 15, 2022. Early adoption is allowed. The Company plans to adopt ASU 2016-02, and related amendments, on January 1, 2021 using the modified retrospective approach transition method as of the date of adoption. The Company will also elect a package of practical expedients, under which an entity need not reassess whether any expired or existing contracts are or contain leases, the lease classification for any expired or existing leases, or initial direct costs for any existing leases. Upon adoption of the new standard, the Company expects to recognize a lease liability and related right of-use asset on the consolidated balance sheet of approximately \$49.7 million and \$33.4 million, respectively.

In June 2016, the FASB issued ASU 2016-13, Financial Instruments – Credit Losses (Topic 326). The new standard adjusts the accounting for assets held at amortized costs basis, including marketable securities accounted for as available-for-sale. The standard eliminates the probable initial recognition threshold and requires an entity to reflect its current estimate of all expected credit losses. The allowance for credit losses is a valuation account that is deducted from the amortized cost basis of the financial assets to present the net amount expected to be collected. For public entities, the guidance was effective for annual reporting periods beginning after December 15, 2019 and for interim periods within those fiscal years. For nonpublic entities, the guidance was effective for annual reporting periods beginning after December 15, 2020. Early adoption was permitted for all entities. In November 2019, the FASB issued ASU 2019-10, which deferred the effective date for nonpublic entities to annual reporting periods beginning after December 15, 2022, including interim periods within those fiscal years. The Company is currently evaluating when to adopt the guidance and the impact the guidance will have on its consolidated financial statements.

In December 2019, the FASB issued ASU No. 2019-12, Income Taxes – Simplifying the Accounting for Income Taxes (Topic 740). The amendments in this update simplify the accounting for income taxes by removing certain exceptions to the general principles as well as clarifying and amending existing guidance to improve consistent application. For public entities, the guidance is effective for annual reporting periods beginning after December 15, 2020 and for interim periods within those fiscal years. For nonpublic entities, the guidance is effective for annual reporting periods beginning after December 15, 2021 and to interim periods within fiscal years beginning after December 15, 2022. Early adoption is permitted for all entities. Depending on the amendment, adoption may be applied on the retrospective, modified retrospective or prospective basis. The

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Company is currently evaluating when to adopt the guidance and the impact the guidance will have on its consolidated financial statements.

### 3. Marketable securities and fair value measurements

As of December 31, 2020, marketable securities by security type consisted of the following:

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(in thousands)			
U.S. treasury securities	\$ 129,446	\$ 9	\$ (4)	\$ 129,451
Commercial paper	52,441	—	—	52,441
Corporate debt securities	17,542	4	—	17,546
Totals	<u>\$ 199,429</u>	<u>\$ 13</u>	<u>\$ (4)</u>	<u>\$ 199,438</u>

The Company did not have marketable securities as of December 31, 2019.

The following tables present the Company's assets that are measured at fair value on a recurring basis and their level within the fair value hierarchy, which is described further within Note 2, Summary of Significant Accounting Policies:

	Fair Value Measurements at December 31, 2020 Using:			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Cash equivalents:				
Money market funds	\$ 63,827	\$ —	\$ —	\$ 63,827
Marketable securities:				
U.S. treasury securities	—	129,451	—	129,451
Commercial paper	—	52,441	—	52,441
Corporate debt securities	—	17,546	—	17,546
Totals	<u>\$ 63,827</u>	<u>\$ 199,438</u>	<u>\$ —</u>	<u>\$ 263,265</u>

	Fair Value Measurements at December 31, 2019 Using:			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Cash equivalents:				
Money market funds	\$ 15,076	\$ —	\$ —	\$ 15,076
Totals	<u>\$ 15,076</u>	<u>\$ —</u>	<u>\$ —</u>	<u>\$ 15,076</u>

Money market funds were valued by the Company based on quoted market prices, which represent a Level 1 measurement within the fair value hierarchy. Marketable securities were valued by the Company using quoted prices in active markets for similar securities, which represent a Level 2 measurement within the fair value hierarchy.

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### 4. Property and equipment, net

Property and equipment, net consisted of the following:

	December 31,	
	2020	2019
	(in thousands)	
Laboratory equipment	\$ 9,313	\$ 5,029
Computer equipment and software	848	740
Furniture and fixtures	826	826
Leasehold improvements	17,374	12,993
Construction in progress	1,082	4,487
	29,443	24,075
Less: Accumulated depreciation and amortization	(5,662)	(2,230)
	<u>\$23,781</u>	<u>\$21,845</u>

Depreciation and amortization expense for the years ended December 31, 2020 and 2019 was \$3.4 million and \$1.9 million, respectively.

### 5. Accrued expenses

Accrued expenses consisted of the following:

	December 31,	
	2020	2019
	(in thousands)	
Accrued employee compensation and benefits	\$ 6,150	\$3,255
Accrued external research and development expenses	1,772	1,344
Accrued professional fees	940	619
Deferred rent	1,389	1,370
Other	702	319
	<u>\$10,953</u>	<u>\$6,907</u>

### 6. Convertible preferred stock

Prior to the IPO, the Company had issued Series A convertible preferred stock (the "Series A"), Series B convertible preferred stock (the "Series B") and Series C convertible preferred stock (the "Series C"). Collectively the Series A, Series B and Series C are referred to as the Preferred Stock.

On January 9, 2020, the Company issued and sold 19,936,296 shares of Series C at a price of \$5.5914 per share for gross proceeds of \$111.5 million. The Company incurred issuance costs in connection with this transaction of \$2.6 million.

Upon issuance of each class of Preferred Stock, the Company assessed the embedded conversion and liquidation features of the shares and determined that such features did not require the Company to separately account for these features. The Company also concluded that no beneficial conversion feature existed on the issuance date of each class of Preferred Stock.

Upon the closing of the IPO in June 2020, the Company's Preferred Stock automatically converted into 27,094,085 shares of common stock.

### 7. Equity

As of December 31, 2020, the Company's restated certificate of incorporation authorizes the Company to issue 150,000,000 shares of common stock, par value \$0.0001 per share, and 5,000,000 shares of preferred stock, par value \$0.0001 per share, all of which preferred stock is undesignated.

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Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Holders of common stock are not entitled to receive dividends, unless declared by the board of directors.

### **8. Stock-based compensation**

The Company's 2017 Stock Incentive Plan (the "2017 Plan") provided for the Company to grant incentive or nonstatutory stock options, restricted stock, restricted stock units and other equity awards to employees, non-employees and directors of the Company. In January 2020, the number of shares of common stock authorized for issuance under the 2017 Plan was increased from 8,407,405 shares to 10,275,717 shares.

In May 2020 the Company's board of directors adopted, and in June 2020 the Company's stockholders approved, the 2020 Stock Incentive Plan (the "2020 Plan" and, together with the 2017 Plan the "Plans"), which became effective on June 11, 2020. The 2020 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. Upon effectiveness of the 2020 Plan, the number of shares of common stock reserved for issuance under the 2020 Plan was the sum of (1) 2,547,698 shares; plus (2) the number of shares (up to a maximum of 7,173,014 shares) as was equal to the sum of (x) the number of shares of common stock reserved for issuance under the 2017 Plan that remained available for grant under the 2017 Plan on June 11, 2020 and (y) the number of shares of common stock subject to outstanding awards granted under the 2017 Plan that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right; plus (3) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2021 and continuing until, and including, the fiscal year ending December 31, 2030, equal to the lesser of (i) 4% of the number of shares of common stock outstanding on such date, and (ii) an amount determined by the board of directors. Upon the effectiveness of the 2020 Plan, the Company ceased granting additional awards under the 2017 Plan.

The Plans are administered by the board of directors or, at the discretion of the board of directors, by a committee of the board of directors. The exercise prices, vesting and other restrictions on any award under the Plans are determined at the discretion of the board of directors, or its committee if so delegated. Stock options granted under the Plans with service-based vesting conditions generally vest over four years and expire after ten years. The exercise price for stock options granted is not less than the fair value of common stock as of the date of grant. Prior to the Company's IPO, fair value of common stock was determined by the board of directors. Subsequent to the IPO, fair value of common stock is based on quoted market prices.

As of December 31, 2020, 2,500,761 shares remained available for future issuance under the 2020 Plan. Shares subject to outstanding awards granted under the Plans that expire, terminate or are otherwise surrendered, cancelled, forfeited or repurchased by the Company at their original issuance price pursuant to a contractual repurchase right will be available for future awards under the 2020 Plan. The number of authorized shares reserved for issuance under the 2020 Plan was increased by 1,878,800 shares effective as of January 1, 2021 in accordance with the provisions of the 2020 Plan described above.

#### ***Employee stock purchase plan***

In May 2020 the Company's board of directors adopted, and in June 2020 the Company's stockholders approved, the 2020 Employee Stock Purchase Plan (the "2020 ESPP"), which became effective June 11, 2020. The 2020 ESPP will be administered by the Company's board of directors or by a committee appointed by the board of directors. The 2020 ESPP initially provides participating employees with the opportunity to purchase up to an aggregate of 481,231 shares of common stock. The number of shares of common stock reserved for issuance under the 2020 ESPP will automatically increase on the first day of each fiscal year, beginning with the fiscal year commencing on January 1, 2021 and continuing for each fiscal year until, and including the fiscal year commencing on, January 1, 2030, in an amount equal to the lowest of (1) 1,302,157 shares of common stock, (2) 1% of the number of shares of common stock outstanding on such date, and (3) an amount determined by the

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board of directors. As of December 31, 2020, no offering periods had commenced under the 2020 ESPP and 481,231 shares were available for issuance. The number of authorized shares reserved for issuance under the 2020 ESPP was increased by 469,700 shares effective as of January 1, 2021 in accordance with the provisions of the 2020 ESPP described above.

### **Stock option valuation**

The fair value of stock option grants is estimated using the Black-Scholes option-pricing model. The Company completed its IPO in 2020 and, accordingly, lacks company-specific historical and implied volatility information. Therefore, it estimated its expected stock volatility based on the historical volatility of a publicly traded set of peer companies and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. For options with service-based vesting conditions, the expected term of the Company's stock options was determined utilizing the "simplified" method for awards that qualified as "plain-vanilla" options. The risk-free interest rate was 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. Expected dividend yield was based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The following table presents, on a weighted average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of stock options granted:

	Year Ended December 31,	
	2020	2019
Risk-free interest rate	0.60%	2.00%
Expected volatility	77.30%	75.7%
Expected dividend yield	—	—
Expected term (in years)	6.0	6.0

The following table summarizes the Company's stock option activity since December 31, 2019:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2019	3,373,884	\$ 4.76	8.79	\$ 8,492
Granted	3,090,315	13.40		
Exercised	(792,845)	4.49		
Forfeited	(429,584)	4.73		
Outstanding as of December 31, 2020	<u>5,241,770</u>	\$ 9.89	8.69	\$ 99,467
Vested and expected to vest as of December 31, 2020	4,585,120	\$ 10.57	8.63	\$ 84,238
Options exercisable as of December 31, 2020	1,108,099	\$ 4.54	7.68	\$ 26,388

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had strike prices lower than the fair value of the Company's common stock.

The weighted average grant-date fair value of awards granted during the years ended December 31, 2020 and 2019 was \$10.41 per share and \$4.46 per share, respectively.

The total intrinsic value of stock options exercised during the years ended December 31, 2020 and 2019 was \$20.0 million and \$0.1 million, respectively.



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### **Restricted common stock units**

During the year ended December 31, 2020, the Company issued 26,242 restricted stock units with a fair value of \$0.5 million. The Company did not issue restricted stock units in the year ended December 31, 2019.

### **Restricted common stock**

The following table summarizes the Company's restricted common stock activity since December 31, 2019:

	<u>Shares</u>	<u>Weighted Average Grant Date Fair Value</u>
Unvested restricted common stock as of December 31, 2019	1,705,188	\$ 1.22
Issued	—	—
Vested	(1,022,234)	1.17
Forfeited	(4,819)	1.95
Unvested restricted common stock as of December 31, 2020	<u>678,135</u>	\$ 1.28

The total fair value of restricted common stock vested during the years ended December 31, 2020 and 2019 was approximately \$15.8 million and \$7.0 million, respectively.

### **Stock-Based Compensation**

The Company records compensation cost for all share-based payment arrangements, including employee, non-employee and director stock options and restricted common stock. The Company recorded stock-based compensation expense in the following expense categories of its consolidated statements of operations and comprehensive loss:

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
	(in thousands)	
Research and development expenses	\$ 4,301	\$ 2,753
General and administrative expenses	4,111	1,454
	<u>\$ 8,412</u>	<u>\$ 4,207</u>

As of December 31, 2020, total unrecognized compensation cost related to unvested stock-based awards was \$27.1 million, which is expected to be recognized over a weighted average period of 3.2 years. Additionally, as of December 31, 2020, the Company has unrecognized compensation cost related to unvested stock-based awards with performance-based vesting conditions for which performance has not been deemed probable of \$2.2 million.

## **9. Income taxes**

For the years ended December 31, 2020 and 2019, the Company recorded no income tax benefits for the net operating losses incurred or for the research and development tax credits generated in each year, due to the uncertainty of realizing a benefit from those items. All of the Company's operating losses since inception have been generated in the United States.

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

	Year Ended December 31,	
	2020	2019
Federal statutory income tax rate	(21.0)%	(21.0)%
State income taxes, net of federal benefit	(7.0)	(5.9)
Federal and state research and development tax credits	(4.2)	(5.1)
Stock-based compensation expense	(2.6)	1.0
Other	—	0.2
Change in deferred tax asset valuation allowance	34.8	30.8
Effective income tax rate	<u>0.0%</u>	<u>0.0%</u>

Net deferred tax assets as of December 31, 2020 and 2019 consisted of the following:

	December 31,	
	2020	2019
(in thousands)		
Deferred tax assets:		
Net operating loss carryforwards	\$ 48,280	\$ 25,023
Research and development tax credit carryforwards	9,385	5,998
Deferred rent	4,456	4,740
Other	2,747	1,469
Total deferred tax assets	64,868	37,230
Deferred tax liabilities:		
Property and equipment	(3,900)	(4,117)
Total deferred tax liabilities	(3,900)	(4,117)
Valuation allowance	(60,968)	(33,113)
Net deferred tax assets	<u>\$ —</u>	<u>\$ —</u>

As of December 31, 2020, the Company had federal net operating loss carryforwards of \$177.3 million, which may be available to offset future taxable income, of which \$8.2 million of the total net operating loss carryforwards expire at various dates beginning in 2036, while the remaining \$169.1 million do not expire but may be limited in their usage to an annual deduction equal to 80% of annual taxable income. As of December 31, 2020, the Company had state net operating loss carryforwards of \$174.7 million, which may be available to offset future taxable income and expire at various dates beginning in 2036. In addition, as of December 31, 2020, the Company also had federal and state research and development tax credit carryforwards of \$6.3 million and \$3.9 million, respectively, which may be available to reduce future tax liabilities and expire at various dates beginning in 2036 and 2032, respectively.

Utilization of the U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Section 382 and Section 383 of the Internal Revenue Code of 1986 as amended (the "Code"), and corresponding provisions of state law, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income and tax liabilities. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there

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have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since inception, utilization of the net operating loss carryforwards or research and development tax credit carryforwards may be subject to an annual limitation, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments. Any limitation may result in expiration of a portion of the net operating loss carryforwards or research and development tax credit carryforwards before their utilization. Further, until a study is completed by the Company and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets, which consist primarily of net operating loss carryforwards and research and development tax credit carryforwards. Management has considered the Company's history of cumulative net losses incurred since inception, estimated future taxable income and prudent and feasible tax planning strategies and has concluded that it is more likely than not that the Company will not realize the benefits of federal and state net deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets as of December 31, 2020 and 2019. The Company reevaluates the positive and negative evidence at each reporting period.

The changes in the valuation allowance for deferred tax assets during the year ended December 31, 2020 and 2019 related primarily to the increases in net operating loss carryforwards and research and development tax credit carryforwards. The changes in the valuation allowance for 2020 and 2019 were as follows:

	<u>Year Ended December 31,</u>	
	<u>2020</u>	<u>2019</u>
	(in thousands)	
Valuation allowance as of beginning of year	\$ 33,113	\$ 14,246
Increases recorded to income tax provision	27,855	18,867
Valuation allowance as of end of year	<u>\$ 60,968</u>	<u>\$ 33,113</u>

The Company assesses the uncertainty in its income tax positions to determine whether a tax position of the Company is more likely than not to be sustained upon examination, including resolution of any related appeals or litigation processes, based on the technical merits of the position. For tax positions meeting the more-likely-than-not threshold, the tax amount recognized in the financial statements is reduced by the largest benefit that has a greater than 50% likelihood of being realized upon the ultimate settlement with the relevant taxing authority. No reserve for uncertain tax positions or related interest and penalties has been recorded at December 31, 2020 and 2019.

The Company files income tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. The Company is open to future tax examination under statute from 2017 to the present.

In March 2020, the Coronavirus Aid, Relief, and Economic Security Act (the "CARES Act") was signed into law making several changes to the Code. The changes include, but are not limited to, increasing the limitation on the amount of deductible interest expense, allowing companies to carryback certain net operating losses, and increasing the amount of net operating loss carryforwards that corporations can use to offset taxable income. The tax law changes in the CARES Act did not have a material impact on the Company's income tax provision.

## 10. License agreements

### *NIH*

The Company has an agreement with the U.S. Department of Health and Human Services, as represented by The National Heart, Lung, and Blood Institute, an Institute of the National Institutes of Health ("NIH"), entered into in 2017, pursuant to which NIH granted the Company a non-exclusive license, with the right to grant sublicenses,

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under certain NIH intellectual property related to the Company's ceDNA construct. In July 2019, the agreement was amended to include Association Institut de Myologie, Universite Pierre et Marie Curie, Centre National de la Recherche Scientifique, and Inserm Transfert SA, collectively referred to as the French Institutions, as a licensor.

The Company is obligated to make future milestone payments of up to \$0.4 million per licensed product upon the achievement of specified milestones as well as royalties on a licensed product-by-licensed product and country-by-country basis of a low single digit percentage of annual net sales of licensed products. The Company is obligated to pay a high single-digit royalty percentage of all sublicensing income. The royalties on net sales may be reduced by up to 25% in certain circumstances as defined in the agreement. The Company's royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the expiration of the last-to-expire licensed intellectual property rights in such country. Additionally, the Company is required to reimburse the French Institutions for a portion of certain past and ongoing patent related expenses related to the licensed technology. The agreement requires the Company to use reasonable commercial efforts to meet certain performance milestones and execute a commercial development plan within specified timeframes.

Unless terminated earlier, the agreement remains in effect until the last to expire of the licensed patent rights on a licensed product-by-licensed product and country-by-country basis. NIH and the French Institutions may terminate the agreement if the Company fails to perform its material obligations, including but not limited to its failure to meet the applicable performance milestones despite using commercially reasonable efforts, and has not remediated such deficiency within a specified time period. NIH and the French Institutions can terminate the agreement in the event the Company becomes insolvent, files a petition in bankruptcy, has such a petition filed against it, or determines to file a petition in bankruptcy. In addition, NIH and the French Institutions may terminate the agreement in the event of a material breach by the Company and failure to cure such breach within a certain period of time. The Company is currently in compliance with the terms of the agreement. The Company can voluntarily terminate the agreement with prior notice to NIH and the French Institutions.

During each of the years ended December 31, 2020 and 2019, the Company recorded research and development expense of less than \$0.1 million under this agreement.

### **UMass**

The Company has an agreement with the University of Massachusetts as represented by and solely on behalf of its Medical School ("UMass"), entered into in 2017, pursuant to which UMass granted the Company an exclusive license, with the right to grant sublicenses, under the UMass intellectual property related to the Company's ceDNA construct.

The Company is obligated to make future milestone payments of up to \$0.8 million per licensed product upon the achievement of specified milestones as well as royalties on a licensed product-by-licensed product and country-by-country basis of a low single digit percentage of annual net sales of licensed products, subject to annual minimum royalties as defined in the agreement. Additionally, the Company has agreed to pay a low-to-mid single-digit royalty percentage of all sublicensing income, which will vary depending on when the sublicense agreement to a third party was executed. The milestone payments are non-refundable and non-creditable against any other payments due to UMass under the agreement. The Company's royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the expiration of the last-to-expire licensed intellectual property rights in such country. The agreement requires the Company to use diligent efforts to meet certain performance milestones within specified timeframes.

As part of the arrangement, the Company agreed to issue 125,677 shares of its common stock to UMass. The Company recorded \$0.1 million as research and development expense and additional-paid-in capital at the time of the agreement in 2017, representing the fair value of the common stock at that time. The shares were issued in August 2019.

Unless terminated earlier, the agreement will continue until the last-to-expire valid claim of the licensed patents. UMass may terminate the agreement if the Company fails to perform its material obligations, including but not limited to its failure to meet the applicable performance milestones despite using commercially reasonable

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efforts, and has not remediated such deficiency within a specified time period or negotiated a revised performance timeline. UMass 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 of a material breach by the Company and failure to cure such breach within a certain period of time. The Company is currently in compliance with the terms of the agreement. The Company can voluntarily terminate the agreement with prior notice to UMass.

During each of the years ended December 31, 2020 and 2019, the Company recorded research and development expense of less than \$0.1 million under this agreement.

### **Other license agreements**

The Company has other license agreements under which it may become subject to future additional fees and milestone payments.

### **11. Commitments and contingencies**

The Company leases its office and laboratory space under a noncancelable operating lease that was entered into in August 2018, as amended in July 2019, and expires in 2029. The Company has an option to extend for one additional term of five years at the greater of the then-current base rent, or the then-current fair market value. The lease agreement includes provisions for a free-rent period and annual rent increases, which are accrued or deferred as appropriate such that rent expense for the lease is recognized on a straight-line basis over the lease term (see Note 2). The Company is responsible for real estate taxes, maintenance, and other operating expenses applicable to the leased premises. The lease provides for a tenant improvement allowance, at the cost of the lessor, not to exceed \$14.7 million. Costs incurred by the Company for tenant improvements but not yet reimbursed by the landlord are presented on the accompanying consolidated balance sheets as tenant receivable. The Company posted a customary letter of credit in the amount of approximately \$2.1 million as a security deposit. The letter of credit is subject to increase if the Company were to sublease any portion of the leased premises.

Previously, the Company leased its office and laboratory space under noncancelable operating leases that expired during 2019.

Rent expense for the years ended December 31, 2020 and 2019 was \$7.5 million and \$7.9 million, respectively.

Future minimum lease payments as of December 31, 2020 are as follows:

<u>Year Ending December 31,</u>	<u>(in thousands)</u>
2021	\$ 7,053
2022	7,251
2023	7,441
2024	7,679
2025	7,881
Thereafter	27,570
	<u>\$ 64,875</u>

### **401(k) Plan**

The Company has a defined-contribution plan under Section 401(k) of the Code (the "401(k) Plan"). The 401(k) Plan covers all employees who meet defined minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. In September 2020, the Company adopted a match program, beginning on January 1, 2021, for employee contributions to the 401(k) Plan up to a maximum of four percent of the employee's salary, subject to the maximums established under the Code.

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### **Indemnification agreements**

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, contract research organizations, business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and its executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. The Company has not incurred any material costs as a result of such indemnifications and is not currently aware of any indemnification claims.

### **Legal proceedings**

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, 2020 and 2019.

## **12. Net loss per share**

### **Net loss per share**

The Company has generated a net loss in all periods presented, therefore the basic and diluted net loss per share attributable to common stockholders are the same as the inclusion of the potentially dilutive securities would be anti-dilutive. The Company excluded the following potential common shares, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share attributable to common stockholders for the periods indicated:

	December 31,	
	2020	2019
Convertible preferred stock (as converted to common stock)	—	14,961,027
Unvested restricted common stock	678,135	1,705,188
Unvested restricted common stock units	19,681	—
Stock options to purchase common stock	5,241,770	3,373,884
	<u>5,939,586</u>	<u>20,040,099</u>

## **13. Selected Quarterly Financial Data (Unaudited)**

The following information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair statement of such information:

	Dec. 31, 2020	Sept. 30, 2020	June 30, 2020	March 31, 2020	Dec. 31, 2019	Sept. 30, 2019	June 30, 2019	March 31, 2019
	(in thousands, except per share)							
Total operating expenses	\$ 24,345	\$ 20,969	\$ 17,764	\$ 18,036	\$ 16,158	\$ 16,333	\$ 15,335	\$ 14,476
Loss from operations	(24,345)	(20,969)	(17,764)	(18,036)	(16,158)	(16,333)	(15,335)	(14,476)
Net loss	(24,226)	(20,849)	(17,731)	(17,717)	(16,063)	(16,128)	(15,032)	(14,094)
Basic and diluted net loss per share, basic and diluted	\$ (0.53)	\$ (0.46)	\$ (1.50)	\$ (3.22)	\$ (3.09)	\$ (3.31)	\$ (3.30)	\$ (3.29)

**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 President and Chief Executive Officer and our Chief Financial Officer (our principal executive officer and principal financial and accounting officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2020. 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, 2020, our President and Chief Executive Officer and our Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

**Management’s Annual Report on Internal Control over Financial Reporting**

This annual report does not include a report of management’s assessment regarding internal control over financial reporting or an attestation report of the Company’s independent registered public accounting firm due to a transition period established by rules of the SEC for newly public 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 three months ended December 31, 2020 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

**ITEM 9B. OTHER INFORMATION**

None.

**PART III**

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

The information required by this Item 10 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

**ITEM 11. EXECUTIVE COMPENSATION**

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

**ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS**

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

**ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE**

The information required by this Item 13 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

**ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES**

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders and is incorporated herein by reference.



**PART IV****ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES***1. Financial Statements*

For a list of the financial statements included herein, see Index to the Consolidated Financial Statements on page 152 of this Annual Report, incorporated into this Item by reference.

*2. Financial Statement Schedules*

Financial statement schedules have been omitted because they are either not required or not applicable or the information is included in the consolidated financial statements or the notes thereto.

*3. Exhibits*

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

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

None.

**Exhibit Index**

<b>Exhibit Number</b>	<b>Description</b>
3.1	<a href="#">Restated Certificate of Incorporation of the registrant, effective as of June 16, 2020 (incorporated by reference to Exhibit 3.1 to the registrant's Current Report on Form 8-K, File No. 001-39319, filed June 16, 2020).</a>
3.2	<a href="#">Bylaws of the registrant, effective as of June 16, 2020 (incorporated by reference to Exhibit 3.2 to the registrant's Current Report on Form 8-K, File No. 001-39319, filed June 16, 2020).</a>
4.1	<a href="#">Specimen Stock Certificate evidencing the shares of common stock (incorporated by reference to Exhibit 4.1 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed June 8, 2020).</a>
4.2	<a href="#">Second Amended and Restated Investors' Rights Agreement dated as of January 9, 2020 by and among the registrant and the other parties thereto (incorporated by reference to Exhibit 4.2 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</a>
4.3*	<a href="#">Description of Capital Stock</a>
10.1+	<a href="#">2017 Stock Incentive Plan (incorporated by reference to Exhibit 10.1 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</a>
10.2+	<a href="#">Form of Stock Option Agreement under 2017 Stock Incentive Plan (incorporated by reference to Exhibit 10.2 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</a>
10.3+	<a href="#">Form of Restricted Stock Agreement under 2017 Stock Incentive Plan (incorporated by reference to Exhibit 10.3 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</a>
10.4+	<a href="#">2020 Stock Incentive Plan (incorporated by reference to Exhibit 10.4 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</a>
10.5+	<a href="#">Form of Stock Option Agreement under 2020 Stock Incentive Plan (incorporated by reference to Exhibit 10.5 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</a>

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<u>Exhibit Number</u>	<u>Description</u>
10.6+	<a href="#"><u>Form of Restricted Stock Agreement under 2020 Stock Incentive Plan (incorporated by reference to Exhibit 10.6 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.7+	<a href="#"><u>Form of Restricted Stock Unit Agreement under 2020 Stock Incentive Plan (incorporated by reference to Exhibit 10.7 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.8+	<a href="#"><u>2020 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.8 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.9	<a href="#"><u>Lease, dated August 2, 2018, by and between the registrant and BMR-Rogers Street LLC, as amended (incorporated by reference to Exhibit 10.1 to the registrant's Quarterly Report on Form 10-Q, File No. 001-39319, filed August 11, 2020).</u></a>
10.10	<a href="#"><u>Form of Indemnification Agreement between the registrant and each of its executive officers and directors (incorporated by reference to Exhibit 10.10 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.11†	<a href="#"><u>Exclusive License Agreement, dated June 28, 2017, by and between the registrant and the University of Massachusetts, as amended (incorporated by reference to Exhibit 10.11 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.12†	<a href="#"><u>Public Health Service Patent License Agreement Nonexclusive Sublicensable, dated February 2, 2017, by and between the registrant and the U.S. Department of Health and Human Services, as represented by the National Heart, Lung, and Blood Institute, as amended on June 20, 2019 (incorporated by reference to Exhibit 10.12 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.13+	<a href="#"><u>Offer letter, dated October 12, 2017, by and between the registrant and Geoff McDonough (incorporated by reference to Exhibit 10.13 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.14+	<a href="#"><u>Offer letter, dated June 25, 2017, by and between the registrant and Douglas Kerr (incorporated by reference to Exhibit 10.14 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.15+	<a href="#"><u>Offer letter, dated June 19, 2020, by and between the registrant and Matthew Norkunas, as amended July 6, 2020 (incorporated by reference to Exhibit 10.2 to the registrant's Quarterly Report on Form 10-Q, File No. 001-39319, filed August 11, 2020).</u></a>
10.16+	<a href="#"><u>Form of Severance Plan Benefit Agreement by and between the registrant and certain of its executive officers (incorporated by reference to Exhibit 10.19 to the registrant's Registration Statement on Form S-1, File No. 333-238608, filed May 22, 2020).</u></a>
10.17+	<a href="#"><u>Offer letter, dated August 26, 2018, by and between the registrant and Tracy Zimmermann, as modified by Promotion letter, dated November 10, 2020 (incorporated by reference to Exhibit 10.20 to the registrant's Registration Statement on Form S-1, File No. 333-251872, filed January 4, 2021).</u></a>
21.1*	<a href="#"><u>Subsidiaries of the registrant.</u></a>
23.1*	<a href="#"><u>Consent of Ernst &amp; Young LLP</u></a>
31.1*	<a href="#"><u>Certification of Principal Executive Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u></a>
31.2*	<a href="#"><u>Certification of Principal Financial Officer pursuant to Rule 13a-14(a) of the Securities Exchange Act, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002</u></a>

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<u>Exhibit Number</u>	<u>Description</u>
32.1**	<a href="#"><u>Certification of Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002</u></a>
32.2**	<a href="#"><u>Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002</u></a>
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

\* Filed herewith.

\*\* Furnished herewith.

† Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

+ Indicates management contract or compensatory plan.

**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.

**GENERATION BIO CO.**

Date: March 18, 2021

By: /s/ Matthew Norkunas  
Matthew Norkunas, M.D., MBA  
Chief Financial Officer  
(Principal Financial and Accounting Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Geoff McDonough</u> Geoff McDonough, M.D.	President, Chief Executive Officer and Director (Principal Executive Officer)	March 18, 2021
<u>/s/ Matthew Norkunas</u> Matthew Norkunas, M.D., MBA	Chief Financial Officer (Principal Financial and Accounting Officer)	March 18, 2021
<u>/s/ Gustav Christensen</u> Gustav Christensen	Director	March 18, 2021
<u>/s/ Ron H.W. Cooper</u> Ron H.W. Cooper	Director	March 18, 2021
<u>/s/ Jeffrey Jonas</u> Jeffrey Jonas, M.D.	Director	March 18, 2021
<u>/s/ Donald Nicholson</u> Donald Nicholson, Ph.D.	Director	March 18, 2021
<u>/s/ Anthony Quinn</u> Anthony Quinn, M.B. Ch.B., Ph.D.	Director	March 18, 2021
<u>/s/ Jason Rhodes</u> Jason Rhodes	Director	March 18, 2021
<u>/s/ Charles Rowland</u> Charles Rowland	Director	March 18, 2021
<u>/s/ Catherine Stehman-Breen</u> Catherine Stehman-Breen, M.D.	Director	March 18, 2021

**DESCRIPTION OF REGISTRANT’S SECURITIES  
REGISTERED PURSUANT TO SECTION 12 OF THE  
SECURITIES EXCHANGE ACT OF 1934, AS AMENDED**

The following description of the capital stock and provisions of Generation Bio Co.’s (the “Company,” “we,” “us” and/or “our”) restated certificate of incorporation and amended and restated bylaws are summaries and are qualified by reference to our restated certificate of incorporation and amended and restated bylaws, each of which is filed as an exhibit to our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission. For additional information, please read our restated certificate of incorporation and amended and restated bylaws and the applicable provisions of the Delaware General Corporation Law.

**General**

Our authorized capital stock consists of 150,000,000 shares of our common stock, par value \$0.0001 per share, and 5,000,000 shares of our preferred stock, par value \$0.0001 per share, all of which preferred stock is undesignated. Our common stock is registered under Section 12(b) of the Securities Exchange Act of 1934, as amended (the “Exchange Act”).

**Common stock**

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. Each election of directors by our stockholders will be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock that we may designate and issue in the future.

In the event of our liquidation or dissolution, the holders of our common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any of our outstanding preferred stock. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate and issue in the future.

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. Our common stock is listed on the Nasdaq Global Select Market under the symbol “GBIO.”

**Preferred stock**

Under the terms of our restated certificate of incorporation, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. There are no shares of preferred stock currently outstanding, and we have no present plans to issue any shares of preferred stock.

**Delaware anti-takeover law and certain charter and bylaw provisions**

***Delaware law***

We are subject to Section 203 of the Delaware General Corporation Law. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a “business combination” with any “interested stockholder” for three years following the date that the person became an interested stockholder, unless either the interested stockholder attained such status with the approval of our board of directors, the business combination is

approved by our board of directors and stockholders in a prescribed manner or the interested stockholder acquired at least 85% of our outstanding voting stock in the transaction in which it became an interested stockholder. A “business combination” includes, among other things, a merger or consolidation involving us and the “interested stockholder” and the sale of more than 10% of our assets. In general, an “interested stockholder” is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

### ***Staggered board; removal of directors***

Our restated certificate of incorporation and our amended and restated bylaws divide our board of directors into three classes with staggered three-year terms. In addition, our restated certificate of incorporation and our amended and restated bylaws provide that directors may be removed only for cause and only by the affirmative vote of the holders of at least 75% of our shares of capital stock present in person or by proxy and entitled to vote. Under our restated certificate of incorporation and our amended and restated bylaws, any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may be filled only by vote of a majority of our directors then in office.

Furthermore, our restated certificate of incorporation provides that the authorized number of directors may be changed only by the resolution of our board of directors. The classification of our board of directors and the limitations on the ability of our stockholders to remove directors, change the authorized number of directors and fill vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

### ***Super-majority voting***

The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation’s certificate of incorporation or bylaws, unless a corporation’s certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our amended and restated bylaws may be amended or repealed by a majority vote of our board of directors or the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all our stockholders would be entitled to cast in any election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our restated certificate of incorporation described above.

### ***Stockholder action; special meeting of stockholders; advance notice requirements for stockholder proposals and director nominations***

Our restated certificate of incorporation and our amended and restated bylaws provide that any action required or permitted to be taken by our stockholders at an annual meeting or special meeting of stockholders may only be taken if it is properly brought before such meeting and may not be taken by written action in lieu of a meeting. Our restated certificate of incorporation and our amended and restated bylaws also provide that, except as otherwise required by law, special meetings of the stockholders can only be called by our board of directors. In addition, our amended and restated bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of candidates for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors, or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder’s intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities. These provisions also could discourage a third party from making a tender offer for our common stock because even if the third party acquired a majority of our outstanding voting stock, it would be able to take action as a stockholder, such as electing new directors or approving a merger, only at a duly called stockholders meeting and not by written consent.

### ***Exclusive forum provision***

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not

have jurisdiction, the federal district court for the District of Delaware) shall be the sole and exclusive forum for the following types of proceedings: (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the General Corporation Law of the State of Delaware or as to which the General Corporation Law of the State of Delaware confers jurisdiction on the Court of Chancery of the State of Delaware, or (4) any action asserting a claim arising pursuant to any provision of our restated certificate of incorporation or our amended and restated bylaws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. These choice of forum provisions will not apply to suits brought to enforce a duty or liability created by the Securities Act, the Exchange Act or any other claim for which federal courts have exclusive jurisdiction. Furthermore, our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act. Although our restated certificate of incorporation contains the choice of forum provisions described above, it is possible that a court could rule that such provisions are inapplicable for a particular claim or action or that such provisions are unenforceable.

**Subsidiaries of the Registrant**

<u>Entity</u>	<u>Jurisdiction of Incorporation</u>
Generation Bio Securities Corporation	Massachusetts



**Consent of Independent Registered Public Accounting Firm**

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-239116) pertaining to the 2017 Stock Incentive Plan, 2020 Stock Incentive Plan and 2020 Employee Stock Purchase Plan of Generation Bio Co. of our report dated March 18, 2021, with respect to the consolidated financial statements of Generation Bio Co. included in this Annual Report (Form 10-K) for the year ended December 31, 2020.

/s/ Ernst & Young LLP

Boston, Massachusetts  
March 18, 2021

**CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER  
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Geoff McDonough, hereby certify that:

1. I have reviewed this Annual Report on Form 10-K of Generation Bio Co.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:
  - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
  - (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
  - (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
  - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
  - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 18, 2021

/s/ Geoff McDonough

Geoff McDonough, M.D.  
President and Chief Executive Officer  
(Principal Executive Officer)

**CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER  
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Matthew Norkunas, hereby certify that:

1. I have reviewed this Annual Report on Form 10-K of Generation Bio Co.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:
  - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
  - (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
  - (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
  - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
  - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 18, 2021

/s/ Matthew Norkunas

Matthew Norkunas, M.D., M.B.A.

Chief Financial Officer

(Principal Financial and Accounting Officer)

**CERTIFICATION OF CHIEF EXECUTIVE OFFICER  
PURSUANT TO 18 U.S.C. SECTION 1350,  
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

I, Geoff McDonough, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, the Annual Report on Form 10-K of Generation Bio Co. for the fiscal year ended December 31, 2020 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Generation Bio Co.

/s/ Geoff McDonough

Geoff McDonough, M.D.

President and Chief Executive Officer

(Principal Executive Officer)

March 18, 2021

**CERTIFICATION OF CHIEF FINANCIAL OFFICER  
PURSUANT TO 18 U.S.C. SECTION 1350,  
AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

I, Matthew Norkunas, certify pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to my knowledge, the Annual Report on Form 10-K of Generation Bio Co. for the fiscal year ended December 31, 2020 fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934 and the information contained in such Form 10-K fairly presents, in all material respects, the financial condition and results of operations of Generation Bio Co.

/s/ Matthew Norkunas

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Matthew Norkunas, M.D., M.B.A.

Chief Financial Officer

(Principal Financial and Accounting Officer)

March 18, 2021