

**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, 2021

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 001-39208

**Beam Therapeutics Inc.**

(Exact name of Registrant as specified in its Charter)

Delaware  
(State or other jurisdiction of  
incorporation or organization)

238 Main Street  
Cambridge, MA  
(Address of principal executive offices)

81-5238376  
(I.R.S. Employer  
Identification No.)

02142  
(Zip Code)

Registrant's telephone number, including area code: 857-327-8775  
Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value \$0.01 per share	BEAM	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 15(d) of the Act. Yes  No

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

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

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

Large accelerated filer	<input checked="" type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input type="checkbox"/>	Smaller reporting company	<input type="checkbox"/>
		Emerging growth company	<input 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 the voting and non-voting common stock held by non-affiliates of the registrant was \$6.45 billion, based on the closing price of the registrant's common stock on Nasdaq on June 30, 2021, the last business day of the registrant's most recently completed second quarter.

The number of shares of registrant's common stock outstanding as of February 22, 2022 was 68,730,340.

**DOCUMENTS INCORPORATED BY REFERENCE**

Registrant incorporates by reference into Part III (Items 10, 11, 12, 13 and 14) of this Annual Report on Form 10-K portions of the Registrant's definitive Proxy Statement for the 2022 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A.

## Table of Contents

	<u>Page</u>
<a href="#"><u>FORWARD-LOOKING STATEMENTS</u></a>	1
<a href="#"><u>RISK FACTORS SUMMARY</u></a>	2
PART I	
Item 1. <a href="#"><u>Business</u></a>	4
Item 1A. <a href="#"><u>Risk Factors</u></a>	50
Item 1B. <a href="#"><u>Unresolved Staff Comments</u></a>	108
Item 2. <a href="#"><u>Properties</u></a>	108
Item 3. <a href="#"><u>Legal Proceedings</u></a>	108
Item 4. <a href="#"><u>Mine Safety Disclosures</u></a>	108
PART II	
Item 5. <a href="#"><u>Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u></a>	109
Item 6. <a href="#"><u>[Reserved]</u></a>	111
Item 7. <a href="#"><u>Management’s Discussion and Analysis of Financial Condition and Results of Operations</u></a>	112
Item 7A. <a href="#"><u>Quantitative and Qualitative Disclosures About Market Risk</u></a>	126
Item 8. <a href="#"><u>Financial Statements and Supplementary Data</u></a>	126
Item 9. <a href="#"><u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u></a>	126
Item 9A. <a href="#"><u>Controls and Procedures</u></a>	126
Item 9B. <a href="#"><u>Other Information</u></a>	128
Item 9C. <a href="#"><u>Disclosure Regarding Foreign Jurisdictions That Prevent Inspections</u></a>	128
PART III	
Item 10. <a href="#"><u>Directors, Executive Officers and Corporate Governance</u></a>	129
Item 11. <a href="#"><u>Executive Compensation</u></a>	129
Item 12. <a href="#"><u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u></a>	129
Item 13. <a href="#"><u>Certain Relationships and Related Transactions, and Director Independence</u></a>	129
Item 14. <a href="#"><u>Principal Accounting Fees and Services</u></a>	129
PART IV	
Item 15. <a href="#"><u>Exhibits, Financial Statement Schedules</u></a>	130
Item 16. <a href="#"><u>Form 10-K Summary</u></a>	133

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## CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Such forward-looking statements reflect, among other things, our current expectations and anticipated results of operations, all of which are subject to known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements, market trends, or industry results to differ materially from those expressed or implied by such forward-looking statements. Therefore, any statements contained herein that are not statements of historical fact may be forward-looking statements and should be evaluated as such. Without limiting the foregoing, the words “anticipate,” “expect,” “suggest,” “plan,” “believe,” “intend,” “project,” “forecast,” “estimates,” “targets,” “projections,” “should,” “could,” “would,” “may,” “might,” “will,” and the negative thereof and similar words and expressions are intended to identify forward-looking statements. These forward-looking statements are subject to a number of important risks, uncertainties and assumptions, including those described in “Risk Factors Summary” and in “Risk Factors” in Part I, Item 1A of this report. Unless legally required, we assume no obligation to update any such forward-looking information to reflect actual results or changes in the factors affecting such forward-looking information. These forward-looking statements reflect, among other things:

- our current expectations and anticipated results of operations;
- our expectations regarding the initiation, timing, progress and results of our research and development programs and preclinical studies, including our expectations that we will submit an Investigational New Drug application, or IND, for BEAM-102 for the treatment of sickle cell disease and BEAM-201 for the treatment of relapsed/refractory T-cell acute lymphoblastic leukemia, that we will initiate IND-enabling studies for BEAM-301 for the treatment Glycogen Storage Disease Type IA (R83C mutation) and that we will nominate a CAR-T development candidate and an additional *in vivo* liver development candidate during 2022;
- our expectations regarding the initiation, timing, progress and results of our clinical trials, including our Phase 1/2 clinical trial designed to assess the safety and efficacy of BEAM-101 for the treatment of sickle cell disease, which we refer to as our BEACON-101 trial;
- our ability to develop and maintain a sustainable portfolio of product candidates;
- our ability to develop life-long, curative, precision genetic medicines for patients through base editing;
- our ability to create a hub for partnering with other companies;
- our plans for preclinical studies for product candidates in our pipeline;
- our ability to advance any product candidates that we may develop and successfully complete any clinical trials or preclinical studies, including the manufacture of any such product candidates;
- our ability to pursue a broad suite of clinically validated delivery modalities;
- our expectations regarding our ability to generate additional novel lipid nanoparticles that we believe could accelerate novel nonviral delivery of gene editing or other nucleic acid payloads to tissues beyond the liver and our ability to expand the reach of our programs, including as a result of our acquisition of Guide Therapeutics, Inc., or Guide;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- developments related to our competitors and our industry;
- the expected timing, progress and success of our collaborations with third parties, including any future payments we may receive under our collaboration and license agreements, and our ability to identify and enter into future license agreements and collaborations;
- developments related to base editing technologies;
- our ability to successfully develop our delivery modalities and obtain and maintain approval for our product candidates;
- our ability to successfully establish and maintain a commercial-scale current Good Manufacturing Practice, or cGMP, manufacturing facility and our expectations that this facility will be operational in the first quarter of 2023;
- regulatory developments in the United States and foreign countries;
- our ability to attract and retain key scientific and management personnel;

- our expectations regarding the strategic and other potential benefits of our acquisition of Guide; and
- the impact of the coronavirus disease of 2019, or COVID-19, pandemic on our business.

When we use the terms “Beam,” the “Company,” “we,” “us” or “our” in this Annual Report on Form 10-K, we mean Beam Therapeutics Inc. and its subsidiaries on a consolidated basis, unless the context indicates otherwise.

## **TRADEMARKS**

We use BEAM, REPAIR and RESCUE and other marks as trademarks in the United States and/or in other countries. This Annual Report on Form 10-K contains references to our trademarks and service marks and to those belonging to other entities. Solely for convenience, trademarks and trade names referred to in this report, including logos, artwork and other visual displays, may appear without the ® or TM symbols, but such references are not intended to indicate in any way that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other entities’ trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, any other entity.

## **MARKET AND INDUSTRY DATA**

Unless otherwise indicated, information contained in this Annual Report on Form 10-K concerning our industry and the markets in which we operate, including our general expectations, market position and market opportunity, is based on our management’s estimates and research, as well as industry and general publications and research, surveys and studies conducted by third parties. We believe that the information from these third-party publications, research, surveys and studies included in this report is reliable. Management’s estimates are derived from publicly available information, their knowledge of our industry and their assumptions based on such information and knowledge, which we believe to be reasonable. This data involves a number of assumptions and limitations which are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in “Risk Factors Summary” and “Risk Factors” in Part I, Item 1A of this report. These and other factors could cause our future performance to differ materially from our assumptions and estimates.

## **RISK FACTORS SUMMARY**

An investment in our common stock involves risks. You should consider carefully the following risks, which are discussed more fully in “Item 1.A. Risk Factors”, and all of the other information contained in this Annual Report on Form 10-K before investing in our common stock. These risks include, but are not limited to, the following:

- Base editing is a novel technology that is not yet clinically validated for human therapeutic use. The approaches we are taking to discover and develop novel therapeutics are unproven and may never lead to marketable products.
- We have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.
- We will need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce, or eliminate our research and product development programs or future commercialization efforts.
- Our short operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.
- We may not be successful in our efforts to identify and develop potential product candidates. If these efforts are unsuccessful, we may never become a commercial stage company or generate any revenues.
- We are very early in our development efforts. Nearly all of our product candidates are still in preclinical development or earlier stages and it will be many years before we or our collaborators commercialize a product candidate, if ever. If we are unable to advance our product candidates to and through clinical development, obtain regulatory approval and ultimately commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.
- If any of the product candidates we may develop or the delivery modalities we rely on cause serious adverse events, undesirable side effects or unexpected characteristics, such events, side effects or characteristics could delay or prevent regulatory approval of the product candidates, limit the commercial potential, or result in significant negative consequences following any potential marketing approval.
- We face significant competition in an environment of rapid technological change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer or more advanced or effective than ours, which may harm our financial condition and our ability to successfully market or commercialize any product candidates we may develop.

- The continuing effects and impacts of the COVID-19 pandemic could have a material adverse effect on our business, financial condition, results of operations and growth prospects.
- We have not tested any of our proposed delivery modalities and product candidates in clinical trials and any favorable preclinical results are not predictive of results that may be observed in clinical trials.
- Adverse public perception of genetic medicines, and gene editing and base editing in particular, may negatively impact regulatory approval of, and/or demand for, our potential products.
- The gene editing field is relatively new and is evolving rapidly. We are focusing our research and development efforts on gene editing using base editing technology, but other gene editing technologies may be discovered that provide significant advantages over base editing, which could materially harm our business.
- Regulatory requirements governing genetic medicines, and in particular any novel genetic medicines we may develop, have changed frequently and may continue to change in the future.
- Genetic medicines are novel, and any product candidates we develop may be complex and difficult to manufacture. We could experience delays in satisfying regulatory authorities or production problems that result in delays in our development or commercialization programs, limit the supply of our product candidates we may develop, or otherwise harm our business.
- We contract with third parties for the manufacture of materials for our research programs, preclinical studies and clinical trial and expect to continue to do so for at least a portion of the manufacturing process for our research programs, preclinical studies, clinical trials and for commercialization of any product candidates that we may develop. This reliance on third parties increases the risk that we will not have sufficient quantities of such materials, product candidates, or any medicines that we may develop and commercialize, or that such supply will not be available to us at an acceptable cost, which could delay, prevent, or impair our development or commercialization efforts.
- Because we are developing product candidates in the field of genetics medicines, a field that includes gene therapy and gene editing, in which there is little clinical experience, there is increased risk that the U.S. Food and Drug Administration, the European Medicines Agency or other regulatory authorities may not consider the endpoints of our clinical trials to provide clinically meaningful results and that these results may be difficult to analyze.
- If we are unable to obtain and maintain patent protection for any product candidates we develop and for our technology, or if the scope of the patent protection obtained is not sufficiently broad, or if we or our licensors are unable to successfully defend our or our licensors' patents against third-party challenges or enforce our or our licensors' patents against third parties 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 our technology may be adversely affected.
- Our rights to develop and commercialize technology and product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.
- The intellectual property landscape around gene editing technology, including base editing and delivery technology, is highly dynamic, and 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 may prevent, delay or otherwise interfere with our product discovery and development efforts.
- Our activities rely on information technology in our own systems and those of our business partners. These systems are subject to a wide and growing variety of cybersecurity risks that may adversely impact our business activities or our ability to engage in various transactions to support our business activities.
- Our clinical research activities depend on the use and disclosure of personal data related to individuals participating in our clinical trials. The rules addressing this data are changing across the world, and these rules may adversely impact our ability to identify individuals for clinical trials or conduct our trials.
- Our owned and in-licensed patents and other intellectual property may be subject to priority disputes or inventorship disputes or we may be subject to claims that we have infringed, misappropriated or otherwise violated the intellectual property of a third party and similar proceedings. If we or our licensors are unsuccessful in any of these proceedings, we may be required to obtain licenses from third parties, which may not be available on commercially reasonable terms or at all, or to cease the development, manufacture, and commercialization of one or more of the product candidates we may develop, which could have a material adverse impact on our business.

**Item 1. Business.****Overview**

We are a biotechnology company committed to establishing the leading, fully integrated platform for precision genetic medicines. Our vision is to provide life-long cures to patients suffering from serious diseases. To achieve this vision, we have assembled a platform that includes a suite of gene editing and delivery technologies and are in the process of developing internal manufacturing capabilities.

Our suite of gene editing technologies is anchored by our proprietary base editing technology, which potentially enables a differentiated class of precision genetic medicines that target a single base in the genome without making a double-stranded break in the DNA. This approach uses a chemical reaction designed to create precise, predictable and efficient genetic outcomes at the targeted sequence. Our proprietary base editors have two principal components: (i) a clustered regularly interspaced short palindromic repeats, or CRISPR, protein, bound to a guide RNA, that leverages the established DNA-targeting ability of CRISPR, but is modified to not cause a double-stranded break, and (ii) a base editing enzyme, such as a deaminase, which carries out the desired chemical modification of the target DNA base. We believe this design contributes to a more precise and efficient edit compared to traditional gene editing methods, which operate by creating targeted double-stranded breaks in the DNA that can result in unwanted DNA modifications. We believe that the precision of our editors will dramatically increase the impact of gene editing for a broad range of therapeutic applications.

To unlock the full potential of our base editing technology across a wide range of therapeutic applications, we are pursuing a broad suite of both clinically validated and novel delivery modalities, depending on tissue type, including: (1) electroporation for efficient delivery to blood cells and immune cells *ex vivo*; (2) lipid nanoparticles, or LNPs, for non-viral *in vivo* delivery to the liver and potentially other organs in the future; and (3) adeno-associated viral vectors, or AAV, for *in vivo* viral delivery to the eye and potentially other organs.

The elegance of the base editing approach combined with a tissue specific delivery modality provides the basis for a targeted efficient, precise, and highly versatile gene editing system, capable of gene correction, gene modification, gene silencing or gene activation, and/or multiplex editing of several genes simultaneously. We are currently advancing a broad, diversified portfolio of base editing programs against distinct editing targets, utilizing the full range of our development capabilities. Furthermore, in addition to our portfolio, we are also pursuing an innovative, platform-based business model with the goal of further expanding our access to new technologies in genetic medicine and increasing the reach of our programs to more patients. Overall, we are seeking to build the leading integrated platform for precision genetic medicine, which may have broad therapeutic applicability and the potential to transform the field of precision genetic medicines.

We continue to make meaningful advancements across our programs. We have identified four development candidates to date: three from our *ex vivo* platform, with two candidates targeting hemoglobinopathies and one candidate targeting T-cell leukemia, and one from our *in vivo* platform targeting glycogen storage disease:

- BEAM-101, our patient-specific, autologous hematopoietic investigational cell therapy, is designed to reproduce single base changes seen in individuals with Hereditary Persistence of Fetal Hemoglobin, or HFPFH, to potentially protect them from the effects of mutations causing sickle cell disease or beta thalassemia by increasing their levels of fetal hemoglobin. We have achieved proof-of-concept *in vivo* with long-term engraftment of base edited human CD34 cells in mice administered BEAM-101. Persistence of engraftment and high levels of editing have been confirmed in several other preclinical studies, including in studies using material generated at a clinically relevant scale. In November 2021, we announced that our Investigational New Drug application, or IND, for BEAM-101 for the treatment of sickle cell disease was cleared by the U.S. Food and Drug Administration, or FDA. We are currently preparing to initiate our BEAM-101 trial, a Phase 1/2 clinical trial designed to assess the safety and efficacy of BEAM-101 for the treatment of sickle cell disease. We have begun site selection and the institutional review board approval processes for this trial and plan to enroll the first subject in the second half of 2022.
- BEAM-102, our second investigational base editing approach for sickle cell disease, is designed to directly correct the causative mutation in sickle cell disease by recreating a naturally-occurring normal human hemoglobin variant, HbG-Makassar. In preclinical studies of BEAM-102, we have demonstrated that our adenine base editors, or ABEs, can efficiently convert the causative Hemoglobin S, or HbS, point mutation, to HbG-Makassar, with high editing efficiency (more than 80%). In these studies, the Makassar variant did not cause hemoglobin to polymerize and red blood cells to sickle under hypoxic conditions and, therefore, edited cells behaved similarly to normal red blood cells with elimination of the disease-causing HbS. The results from these studies support the conclusion that the Makassar variant is able to protect cells from sickling, even in the context of mono-allelic editing (with one sickle allele and one corrected allele). We initiated IND-enabling studies for BEAM-102 during 2021 and expect to submit an IND to the FDA for the treatment of sickle cell disease during the second half of 2022.

- BEAM-201 is a potent and specific anti-CD7, multiplex-edited, allogeneic chimeric antigen receptor T cell, or CAR-T, development candidate for the treatment of relapsed/refractory T-cell acute lymphoblastic leukemia/T cell lymphoblastic lymphoma, or T-ALL/T-LL, a severe disease affecting children and adults with a five-year overall survival rate of less than 25%. BEAM-201 is produced using a Good Manufacturing Practice, or GMP, compliant, clinical-scale process in which T-cells derived from healthy donors are simultaneously base edited at four genomic loci, then transduced with a lentivirus coding for an anti-CD7 CAR. The resulting cells are designed to be universally-compatible, allogeneic (“off the shelf”) CD7-targeting CAR-T cells, resistant to both fratricide and immunosuppression. We initiated IND-enabling studies for BEAM-201 during 2021 and expect to submit an IND to the FDA for the treatment of relapsed, refractory T-ALL/T-LL during the second half of 2022.
- BEAM-301, our first liver-targeted development candidate, is designed to apply base editing via LNP delivery to repair the R83C mutation of the G6PC gene, one of the most prevalent causes of Glycogen Storage Disease Type Ia, or GSDIa. In October 2021, we presented preclinical data demonstrating that administration of our LNP-delivered ABEs in a newborn humanized GSDIa R83C mouse model resulted in normal growth to the end of the study at three weeks of age and normalization of these subjects' metabolic profile (glucose and lipids). In contrast, homozygous animals died shortly after birth in the absence of glucose supplementation. In addition, we observed editing efficiencies up to approximately 60% by next generation sequencing of DNA isolated from the whole liver. Published third party studies suggest that normal G6Pase activity of approximately 11% in the liver is sufficient to mitigate fasting hypoglycemia in animal models of GSDIa. In December 2021, we nominated BEAM-301 as our first development candidate for *in vivo* base editing in the liver using LNP delivery for the treatment of patients with GSDIa (R83C mutation), and anticipate initiating IND-enabling studies for BEAM-301 in 2022.

We also continue to advance numerous other programs in a range of therapeutic areas. We have shown the ability to directly correct the mutation causing alpha-1 antitrypsin deficiency, providing both *in vitro* and *in vivo* preclinical proof-of-concept for base editing to address this disease. We have also achieved editing levels *in vivo*, in preclinical models, for the correction of the Q347X mutation, which is the other most prevalent mutation causing GSDIa, that could be clinically relevant if reproduced in humans. We anticipate nominating a second liver-targeted development candidate in 2022. In addition, in preclinical studies in our multiplex-edited allogeneic CAR-T research program, we have demonstrated knockout of CD5 expression to be a general mechanism to enhance potency and potentially improve durability of highly multiplexed CAR-T cells. We plan to nominate a second CAR-T development candidate, in addition to BEAM-201, in 2022.

The modularity of our platform means that establishing preclinical proof-of-concept of base editing using a particular delivery modality will potentially reduce risk and accelerate the timeline for the development of additional product candidates targeting the same tissue. In some cases, a new product candidate may only require changing the guide RNA. Subsequent programs using the same delivery modality can also take advantage of shared capabilities and resources of earlier programs.

#### **Background on current methods in genetic medicines**

The human genome has four types of bases found in DNA: adenine (A), cytosine (C), guanine (G), and thymine (T). Adenine pairs with thymine, and cytosine pairs with guanine. The genome is comprised of over three billion of these base pairs in two intertwining strands of DNA; the sequence of these bases encodes genes. In a living cell, these DNA sequences are continuously copied into short ribonucleic acid transcripts, called messenger RNA, or mRNA, which are then translated into proteins that perform the functions of life. By precisely modulating the DNA sequence, it is possible to develop different therapeutic approaches. One of these approaches involves correcting misspellings in genes, known as mutations, which can yield proteins that are dysfunctional or missing altogether, causing disease. An additional example, involves modulating genes in immune cells that can improve the ability of these cells to kill certain cancers as, for example, in the case of CAR-T cells.

We believe we are well-positioned to accelerate progression of our base editing programs to clinical trials and through potential approval by leveraging the clinical, regulatory, and manufacturing advancements made to date in the field of genetic medicine as well as the significant internal development capabilities we have established. In addition, we believe the combination of our base editing technology and our proprietary delivery technologies has the potential to provide life-long cures after a single treatment by overcoming challenges associated with current methods in gene editing.

#### **Current challenges in gene editing**

Gene editing works by disrupting, inserting, or modifying genes in the natural context of the genome. The vast majority of established gene editing methods rely on a class of enzymes, called nucleases, to make a double-stranded break in the DNA at a targeted location. These enzymes include CRISPR, Zinc Fingers, Arcuses, and TAL Nucleases, and, while these approaches have distinct technical features relative to each other, they each make the same type of edit and, therefore, share several similar limitations.

First, there is a lack of predictability in genetic outcomes when altering gene sequences with nucleases. The dominant, naturally-occurring DNA repair system that corrects double-stranded breaks within cells is called Non-Homologous End Joining, or NHEJ. This system can patch the broken ends of the chromosomes back together but will simultaneously insert or delete sequences at random near the location where the break occurs. While this NHEJ approach can be effective if the desired outcome is to knock out or switch off the whole gene, it does not allow for precise control of the specific genetic outcome at the target site and its effects may vary from individual to individual.

Second, there are potential toxicities associated with double-stranded breaks, such as activating the cell death response and/or genomic instability. In addition, if the double-stranded break occurs in the wrong place, the break can also lead to unwanted gene disruptions. Multiple edits using NHEJ, and thus multiple double-stranded breaks, can compound this issue and lead to large-scale genomic translocations and rearrangements, potentially limiting the applicability of nuclease-based approaches in multiplex editing.

Third, while gene disruption with nucleases is efficient, making specific sequence changes to correct or modify genes remains largely inefficient. To change a gene sequence, gene editing using nucleases relies on a DNA repair pathway called Homology Directed Repair, or HDR. HDR is a low-efficiency DNA repair pathway, typically yielding single digit percentage editing. This pathway also requires the simultaneous delivery of an additional DNA template containing the desired, corrected gene sequence, which needs to be positioned at the precise location where the double-stranded break has occurred. The requirement of an additional DNA template significantly increases the complexity of delivery. More recently, approaches have been developed to insert sequences into certain highly expressed genes, such as the albumin locus in liver cells. These editing approaches currently can only be used to address diseases that are associated with circulating proteins, and the efficiency of these approaches remains low.

Finally, gene editing through HDR does not allow for the correction of genes in non-dividing cells, since this DNA repair machinery is only expressed in dividing cells, further limiting their applications, given that the majority of cells in the adult body are non-dividing.

### **Base editors: A potential differentiated class of medicines that perform precision chemistry on genes**

Errors of a single base, known as point mutations, are the most common class of genetic mutations, representing approximately 58% of all the known genetic errors associated with disease. Other natural genetic variations of a single base among human populations, revealed by population-level genomic studies, are known to protect against certain diseases. Established gene editing technologies, including CRISPR, Zinc Fingers, Arcuses and TAL Nucleases, typically do not edit at the single base level, due to the low efficiency of HDR. Instead, these technologies operate by creating a targeted double-stranded break in the DNA, and then rely on cellular mechanisms to complete the editing process. Such approaches can be effective in the disruption of gene expression; however, they have limited control of the editing outcome and low efficiency of precise gene correction, and can result in unwanted DNA modifications.

Our base editing technology is a differentiated therapeutic approach, potentially capable of altering the human genome at the foundational level of genetic information – a single base – without making a double-stranded break in the DNA. Base editing involves the enzymatic modification of a single type of base, at a targeted location directly on the gene, specifically C-to-T or A-to-G. The elegance and simplicity of this approach can be thought of as a “pencil,” where the error is erased and the correct letter is written. This approach is designed to create precise, predictable and efficient genetic outcomes at a targeted sequence, which can be used in a variety of editing strategies, including the correction of single mutations or the engineering of advanced cell therapies, aimed at providing a compelling therapeutic benefit. We believe, therefore, that base editors may have broad therapeutic applicability and transformational potential for the field of precision genetic medicines.

### **Advantages of base editing**

We believe our base editing platform offers meaningful advantages over established approaches in gene editing, including:

- Highly precise and predictable gene editing, designed to make only one type of base edit at the desired target location;
- Highly efficient and therapeutically relevant levels of gene correction, which are generally unachievable by nuclease-based editing methods;
- Broad applicability in a wide range of cell types, including both dividing and non-dividing cells;
- Direct chemical modification of DNA with no requirement for delivery of the corrected DNA sequence;
- Avoidance of unwanted DNA modifications associated with double-stranded breaks, including gene disruptions and chromosomal rearrangements, such as translocations or deletions;
- The potential for permanent editing of genes, creating the opportunity for a life-long therapeutic outcome, including the ability to treat infants or young children since the edit will be passed on by dividing cells as the child grows;



- Preservation of natural regulation and a normal number of copies of the gene in the cell by modification of genes in their native genomic setting; and
- A versatile and modular product engine that can target a different gene sequence with the same base editor and a different guide RNA.

### **Our base editing platform**

Our proprietary DNA base editors have two principal components that may be fused together or incorporated into one another to form a single protein: (i) a CRISPR protein, bound to a guide RNA, that leverages the established DNA-targeting ability of CRISPR, but modified to not cause a double-stranded break, and (ii) a base editing enzyme, such as a deaminase, which carries out the desired chemical modification of the target DNA base. This proprietary combination enables the precise and targeted editing of a single base pair of DNA, which has not been previously possible with established gene editing technologies.

CRISPR proteins enable precise targeting of genomic DNA sequences. These proteins have been adapted and engineered over the years to target specific genomic locations with high specificity in human cells. CRISPR proteins incorporate a programmable component called a guide RNA. The guide RNA includes a region of approximately 20 bases, which allows the CRISPR protein to recognize any DNA sequence that is complementary to the guide RNA. This complementary sequence on DNA, also approximately 20 bases, is known as a protospacer. The short sequence of about three bases immediately following the protospacer on the genomic DNA is referred to as the protospacer adjacent motif, or PAM. The presence of the PAM is necessary for RNA-DNA pairing to occur when a matching protospacer sequence is present.

In our base editors, the first component is the CRISPR protein. We currently use a CRISPR associated protein 9, or Cas9, protein for our DNA base editors. We also have ongoing efforts to create base editors with other CRISPR associated, or Cas, proteins, including Cas protein 12b, or Cas12b, a nuclease that is proprietary to Beam. The targeting ability of the CRISPR protein has been preserved, but the cutting ability has been modified such that the CRISPR protein does not make a double-stranded break in the DNA. Our base editors benefit from an additional feature of the CRISPR protein, which, upon binding to its double-stranded DNA target, opens a four to five base single-stranded segment, known as the editing window.

The second component of our base editors is a deaminase, a class of naturally occurring enzymes. For our Cytosine Base Editors, or CBEs, we use a deaminase that is designed to act only on single-stranded DNA. This helps to minimize edits in other parts of the genome, where DNA is predominantly double-stranded. Similarly, for our Adenine Base Editors, or ABEs, we use a different, engineered deaminase that is also designed to act only on single-stranded DNA.

The deaminase makes a predictable chemical modification, called deamination, of the amine group on either adenine or cytosine. The deaminase in a CBE will convert an amine group of C, resulting in the formation of uracil, which is read by the DNA polymerase as a T. Once this strand has been edited, the intermediate DNA consists of an edited strand, containing a U at the target locus, and an unedited strand with a G. The U:G is a mismatch, which the cell will normally attempt to repair in a process that can potentially lose the edit. In order to preserve the editing, we modify the CRISPR in our base editors to cleave the unedited single strand of the DNA, referred to as nicking, rather than creating double-stranded breaks. Nicking is intended to increase the efficiency of editing by inducing the cell to use the newly edited strand, and not the unedited strand, as the template for repair, resulting in a U:A pair without any translocations. Upon DNA repair or replication, the U is read as a T, resulting in a T:A pair, thereby completing the permanent conversion of a C:G base pair to a T:A base pair.

Analogously, when an ABE is used instead of a CBE, the conversion of an amine group of A results in the formation of inosine, which is read by the DNA polymerase as a G, which subsequently leads to an A-to-G change. As a result, an A:T pair is converted to a G:C pair. Because the DNA is double-stranded, by targeting the non-coding strand, we can also convert a T:A pair to a C:G and a G:C pair to a A:T pair in the coding strand. For example, using ABE to install an A-to-G edit on the non-coding strand of the DNA will cause a T-to-C change in the coding sequence of the gene once the base pair has been fully modified.

The modular and individual components of our base editors have the potential to be rapidly customized for specific diseases, potentially allowing us to create new programs with significant efficiencies in development. By changing the guide RNA portions of the CRISPR protein, we believe we can quickly and precisely retarget base editors to different genomic locations based on their gene sequences. By changing the deaminase, for example, we can quickly and precisely retarget which base is edited (e.g., C or A). As a result, we believe our base editing platform is highly versatile, efficient, and scalable for the discovery of drug candidates.

## Diverse therapeutic applications of base editing

We believe the unique advantages of our base editing platform – single base editing precision, predictable editing outcome, high editing efficiency, and the avoidance of double-stranded breaks – make base editing a compelling approach for a wide range of therapeutic applications. This includes gene correction, gene modification, gene silencing and gene activation, as well as multiplex editing of several genes simultaneously.

- **Gene Correction** - Errors of a single base, known as point mutations, are the most common form of genetic mutations, representing approximately 58% of all the known genetic errors associated with disease. For example, sickle cell disease is caused by a single point mutation at position 6 in the adult hemoglobin gene, while alpha-1 antitrypsin deficiency is caused by a single point mutation at position 342 in the SERPINA1 gene. We believe base editors may be an ideal tool for repairing point mutations.
- **Gene Modification** - In addition to repairing point mutations, base editors are also capable of making other kinds of precise modifications to genes that could be used to treat disease. Natural genetic variations of a single base among human populations, revealed by population-level genomic studies, are now known to protect against or modify risk for many diseases, including Alzheimer's disease, cardiovascular disease and liver disease. We believe base editors could potentially prevent or modify risk of disease by making these kinds of precise single-base modifications to genes, informed by human clinical genetics.
- **Gene Silencing or Activation** - Upregulation or downregulation, including silencing and activation, of gene expression is a desirable therapeutic approach to cure many diseases. The high level of precision of base editors is ideally suited to alter regulatory regions of genes, ensuring that only a few bases at precise locations are altered to achieve the desired effect without causing broader disruptions to adjacent regions that may still have important regulatory functions. For example, we have demonstrated in preclinical studies re-activation of expression of fetal hemoglobin by precisely changing the regulatory region of the relevant genes, thus preventing one or more repressor proteins, including B-cell lymphoma/leukemia 11A, from binding. Both our CBEs and ABEs can also be used to silence the expression of genes, with editing rates that are highly comparable to those achieved with nuclease-based editors but without requiring a double-stranded break. Gene silencing, such as targeting surface proteins in a CAR-T cell, can be achieved either by the conversion of certain short gene sequences, called codons, into STOP codons or by the disruption of splice donor-acceptor sites, in each case with a single base conversion.
- **Multiplex base editing** - By avoiding the creation of double-stranded breaks, base editors are particularly advantageous in situations where multiple sequences in the genome must be simultaneously edited. This could include targeting duplicated or repetitive sequences in the genome, as is the case with the identical regulatory regions of the two neighboring genes for fetal hemoglobin, or targeting several genes at once, such as in the creation of advanced cell therapies like CAR-T cells with a combination of features that could dramatically enhance their therapeutic potential. Base editors are designed to not create double-stranded breaks, and we have demonstrated in preclinical cell line studies that they can edit multiple locations simultaneously without causing any detectable chromosomal rearrangements. Additionally, there are manufacturing benefits as cells that have three or more nuclease edits appear to have a significant growth deficit compared to cells that have been edited the same number of times with a base editor. We believe that our base editors can provide a significant and meaningful advancement in therapies where more complex gene editing is required, such as targeting multiple sequences across the genome or creating highly engineered cellular therapies.

## Delivery of genetic medicines

To complement our next-generation gene editing technologies, we are also making significant investments in a broad suite of delivery technologies designed to deliver gene editing or other nucleic acid payloads to the right cells and enable potentially curative therapy. These delivery technologies include *ex vivo* electroporation, nonviral vectors such as LNPs, and viral vectors such as AAVs. In our pipeline, we have initially focused on applications of these technologies where their delivery capabilities have already been clinically-validated by third parties, such as *ex vivo* editing of blood stem cells and LNP delivery to the liver. Longer term, we are also investing in more innovative delivery options, such as LNPs that could target other organs beyond the liver, or novel viral vectors beyond AAV. We have also developed critical enabling capabilities such as mRNA manufacturing and cell processing for autologous and allogeneic cell therapy.

Consistent with this approach, our acquisition of Guide Therapeutics, Inc., or Guide, expanded our ability to explore new tissues and disease indications with our editing technologies. With Guide's proprietary screening technology, which utilizes DNA barcodes to enable high throughput *in vivo* LNP screening, we have a broad library of lipids and lipid formulations, and we have generated additional novel LNPs that we believe can accelerate novel nonviral delivery of gene editing or other nucleic acid payloads to tissues beyond the liver. For example, we have used our DNA barcoding technology to identify a family of LNPs for delivery of base editors to hematopoietic stem and progenitor cells, or HSPCs, in mice, and we have screened more than 1,000 LNPs to identify LNPs that achieve durable, dose-dependent mRNA transfection in HSPCs in mice and non-human primates, or NHPs, in preclinical studies.

## Manufacturing of genetic medicines

To realize the full potential of base editors as a differentiated class of medicines and to enable our parallel investment strategy in multiple delivery modalities, we are building customized and integrated capabilities across discovery, manufacturing, and preclinical and clinical development. Due to the critical importance of high-quality manufacturing and control of production timing and know-how, we have taken steps toward establishing our own manufacturing facility, which will provide us the flexibility to manufacture a variety of different product modalities. We believe this investment will maximize the value of our portfolio and capabilities, the probability of technical success of our programs, and the speed at which we can provide potentially life-long cures to patients.

In August 2020, we entered into a lease agreement with Alexandria Real Estate Equities, Inc. to build a 100,000 square foot current cGMP compliant manufacturing facility in Research Triangle Park, North Carolina intended to support a broad range of clinical programs. We anticipate that the facility will be operational in the first quarter of 2023. The facility is designed to support manufacturing for our *ex vivo* cell therapy programs in hematology and oncology and *in vivo* non-viral delivery programs for liver diseases, with flexibility to support manufacturing of our viral delivery programs, and ultimately, scale-up to support potential commercial supply. For our initial waves of clinical trials, we expect to use CMOs with relevant manufacturing experience in genetic medicines.

### Our platform

In summary, we believe that building an integrated platform combining our gene editing capabilities with advanced delivery and manufacturing capabilities will give us the flexibility to develop a sustainable portfolio, featuring rapid development of new programs and lifecycle improvements in our core programs. For example, for the treatment of sickle cell disease, we are pursuing both an *ex vivo*, autologous transplant-based approach with BEAM-101 and BEAM-102, but also are investing in a potential *in vivo*, LNP-based treatment to reach even more patients – all because we have consolidated both cell-based and novel HSC-targeting LNP technologies internally.

In addition to our internal pipeline, the breadth and depth of our integrated technology platform gives us the opportunity to create a hub for partnering with other companies, which is an important part of our business model. We believe this model will help us to unlock the full potential of precision genetic medicine across a wider array of possible applications.

In some cases, we have established collaborations that advance new programs in “whitespace” areas by giving a collaborator broad access to our various editing and delivery technologies, such as in our Verve collaboration in cardiovascular disease, our Apellis collaboration in complement-mediated disorders, and our Pfizer collaboration in rare diseases of the liver, muscle and central nervous system. In other cases, we have leveraged our team, capabilities and technologies to access other emerging technologies or capabilities, such as in our relationship with Prime Medicine. Our overall goal with these platform activities is to continue expanding our access to the technologies and teams in genetic medicine that will maximize our long-term value creation and impact on patients.

#### Suite of gene editing technologies

- Base editing
- Nuclease editing
- RNA editing
- Prime editing



#### Suite of delivery technologies

- Autologous / allogeneic cell products
- mRNA
- LNP vectors
- Viral vectors

#### Internal manufacturing capability

- 100,000 square foot GMP clinical/commercial facility in NC, phased build, anticipated to be operational in 2023

## Our base editing portfolio

We believe building a diversified portfolio leveraging the full breadth of our editing and delivery technologies in parallel will maximize our ability to provide life-long curative therapies to patients over the broadest possible range of diseases. We plan to advance multiple programs through clinical development in parallel, with each one potentially capable of delivering proof-of-concept in Phase 1 clinical trials in genetically defined patient populations and potentially reaching approval on an accelerated pathway. Our portfolio is purposefully built around a mix of strategic and technical profiles, creating significant optionality and risk diversification. We prioritize and advance programs based on a number of criteria, including significant unmet medical need, editing feasibility, clinically validated delivery modalities, favorable clinical and regulatory development pathways, and evidence that base editing offers potentially compelling advantages for patients over available standards-of-care and novel therapeutic modalities in development.

Our programs are organized by delivery modality: *ex vivo* hematopoietic stem cells, or HSCs, *ex vivo* T cells and *in vivo* using both LNP and AAV delivery technologies. The following table summarizes the status of certain of our programs:

DELIVERY	PROGRAM / DISEASE		EDITING APPROACH	RESEARCH	LEAD OPTIMIZATION	IND ENABLING	PHASE I/II	PIVOTAL
Ex vivo HSCs	BEAM-101	Sickle Cell Disease Beta Thalassemia	Activation of fetal hemoglobin					
	BEAM-102	Sickle Cell Disease	Correction of HbS sickle mutation					
Ex vivo T cells	BEAM-201	T-cell ALL CD7+ AML	Multiplex silenced CD7 CAR-T					
		T-cell Lymphoma	Multiplex silenced CD5 CAR-T					
In vivo LNP	BEAM-301	Glycogen Storage Disease Ia	Correction of R83C mutation					
		Alpha-1 Antitrypsin Deficiency	Correction of E342K mutation					
		Glycogen Storage Disease Ia	Correction of Q347X mutation					
		Hepatitis B Virus	Multiplex silencing					
		Complement Pathway (Apellis)	Undisclosed					
		3 undisclosed targets (Pfizer)	Undisclosed					
AAV		Stargardt Disease	Correction of G1961E mutation					

### Ex Vivo HSCs: Sickle cell disease and beta-thalassemia

We are advancing *ex vivo* base editing programs in which HSCs are collected from a patient, edited using electroporation, a clinically validated technology for the delivery of therapeutic constructs into harvested cells, and then infused back into the patient following a myeloablative conditioning regimen, such as treatment with busulfan, the standard of care in HSC transplantation today. Once reinfused, the HSCs begin repopulating a portion of the bone marrow in a process known as engraftment. The engrafted, edited HSCs give rise to progenitor cell types with the corrected gene sequences. We plan to deploy this *ex vivo* approach in our BEAM-101 (sickle cell disease and beta thalassemia) and BEAM-102 (sickle cell disease) base editing programs.

Sickle cell disease, a severe inherited blood disease, is caused by a single point mutation, E6V, in the beta globin gene. This mutation causes the mutated form of HbS to aggregate into long, rigid molecules that bend red blood cells into a sickle shape under conditions of low oxygen. Sickled cells obstruct blood vessels and die prematurely, ultimately resulting in anemia, severe pain (crises), infections, stroke, organ failure, and early death. Sickle cell disease is the most common inherited blood disorder in the United States, affecting an estimated 100,000 individuals, of which a significant proportion are of African-American descent (1:365 births). Beta-thalassemia is another inherited blood disorder characterized by severe anemia caused by reduced production of functional hemoglobin due to insufficient expression of the beta globin protein. Transfusion-dependent beta-thalassemia, or TDBT, is the most severe form of this disease, often requiring multiple transfusions per year. Patients with TDBT suffer from failure to thrive, persistent infections, and life-threatening anemia. The incidence of symptomatic beta-thalassemia is estimated to be 1:100,000 worldwide, including 1:10,000 in Europe. In the United States, based on affected birth incidence of 0.7 in 100,000 births, and increasing survival rates, we expect the population of individuals affected by this disease to be more than 1,400 and rising. The only potentially curative therapy currently available for patients with sickle cell disease or beta-thalassemia is allogeneic HSC transplantation, or HSCT; however, this procedure holds a high level of risk, particularly Graft-versus-Host Disease resulting in a low number of patients opting for this treatment.

We are pursuing a long-term, staged development strategy for our base editing approach to treat sickle cell disease that consists of advancing our *ex vivo* programs, BEAM-101 and BEAM-102, in Wave 1, improving patient conditioning regimens in Wave 2, and enabling *in vivo* base editing with delivery directly into HSCs of patients via LNPs in Wave 3. We believe this suite of technologies – base editing, improved conditioning and *in vivo* delivery for editing HSCs – can maximize the potential applicability of our sickle cell disease programs to patients as well as create a platform for the treatment of many other severe genetic blood disorders.

#### **Wave 1: Ex Vivo Base Editing via Autologous Transplant with BEAM-101 and BEAM-102**

We are using base editing to pursue the development of two complementary approaches to treating sickle cell disease (BEAM-101 and BEAM-102), and one approach to treat beta-thalassemia (BEAM-101).

##### **BEAM-101: Recreating naturally-occurring protective mutations to activate fetal hemoglobin**

BEAM-101 is an investigational, patient-specific, autologous hematopoietic investigational cell therapy which is designed to incorporate *ex vivo* base edits that mimic single nucleotide polymorphisms seen in individuals with HPFH to potentially alleviate the effects of mutations causing sickle cell disease or beta thalassemia. In November 2021, we announced that our IND for BEAM-101 for the treatment of sickle cell disease was cleared by the FDA. We are preparing to initiate our BEACON-101 trial, a Phase 1/2 clinical trial designed to assess the safety and efficacy of BEAM-101 for the treatment of sickle cell disease. The BEACON-101 trial is expected to include an initial “sentinel” cohort of three patients, treated one at a time to confirm successful engraftment, followed by dosing in up to a total of 45 patients. The clinical trial is designed to initially include patients between ages 18 and 35 with sickle cell disease who have received prior treatment with at least one disease-modifying agent with inadequate response or intolerance. Following mobilization, conditioning and HSC transplant with BEAM-101, patients will be assessed for safety, with safety endpoints including the proportion of patients with successful neutrophil engraftment by day 42 and safety and tolerability assessments, as well as for efficacy, with efficacy endpoints including the change from baseline in severe vaso-occlusive events, transfusion requirements, hemoglobin F levels, and quality of life and ability to function. We have begun site selection and the institutional review board approval processes for the BEACON-101 trial and plan to enroll the first subject in the second half of 2022.

The beneficial effects of the fetal form of hemoglobin, or HbF, to compensate for mutations in adult hemoglobin were first identified in individuals with HPFH. Individuals who carry mutations that would have typically caused them to be beta-thalassemia or sickle cell disease patients, but who also have HPFH, are asymptomatic or experience a much milder form of their disease. HPFH is caused by single base changes in the regulatory region of the genes, HBG1 and HBG2, which prevents binding of one or more repressor proteins and increases the expression of gamma globin, which forms part of the HbF tetramer.

Using base editing, we are attempting to reproduce these specific, naturally occurring base changes in the regulatory elements of the gamma globin genes, preventing binding of repressor proteins and leading to re-activation of gamma globin expression, and thus the increase in gamma globin levels. Our preclinical *in vitro* and *in vivo* characterization of BEAM-101 using *ex vivo* delivery achieved precise and efficient editing of human CD34+ HSPCs, resulting in long-term engraftment and therapeutically-relevant increases in target gene expression in mice. Additionally, there have been no observed guide-dependent or guide-independent off-target events for this program.

##### **Preclinical *in vitro* characterization of BEAM-101:**

- We demonstrated greater than 90% editing in healthy donor CD34 cells *in vitro*.
- We demonstrated gamma globin upregulation following erythroid differentiation is highly correlated ( $R^2=0.993$ ) with editing rates, where, at greater than 90% editing, we achieved a greater than 60% increase in gamma globin in healthy donor CD34+ cells.
- We observed successful editing of CD34+ cells from a homozygous sickle cell disease patient, demonstrating a greater than 60% increase in gamma globin levels with a concomitant decrease to less than 40% sickle beta globin levels *in vitro* after *in vitro* differentiation.

##### **Preclinical *in vivo* performance of BEAM-101:**

- We demonstrated that edited CD34+ cells from a healthy human donor engraft with high chimerism and maintain greater than 90% editing after 16 weeks in immunocompromised mice.
- We demonstrated after 16-week engraftment that base edited cells lead to successful multilineage reconstitution with greater than 90% base editing achieved in sorted human HSPCs, myeloid, lymphoid and erythroid cells.
- We replicated these findings with cells from a second donor at 18 weeks post-engraftment.

### *BEAM-102: Direct correction of the sickle cell mutation*

Our second base editing approach for sickle cell disease, BEAM-102, is designed to directly correct the causative sickle mutation at position 6 of the beta globin gene. By making a single A-to-G edit, we have demonstrated in primary human CD34+ cells isolated from sickle cell disease patients the ability to create the naturally occurring HbG or “Makassar” variant of hemoglobin. This variant, which was identified in humans and first published in 1970, has the same function as the wild-type variant and does not cause sickle cell disease. Distinct from other approaches, cells that are successfully edited in this way are fully corrected, no longer containing the sickle protein. We have initiated IND-enabling studies for BEAM-102 and expect to submit an IND to the FDA for the treatment of sickle cell disease during the second half of 2022.

BEAM-102 uses *ex vivo* delivery of our ABEs to edit CD34+ HSPCs. In cells isolated from donors with sickle cell disease, we achieved greater than 80% correction of the sickle point mutation to the HbG-Makassar variant, following *in vitro* erythroid differentiation. Importantly, we observed a simultaneous reduction of HbS to less than 20% of control levels, a level that is lower than that typically observed in sickle trait individuals, who are asymptomatic. More than 70% of erythroid colonies derived from edited patient cells showed biallelic editing (yielding cells that are potentially cured, no longer producing any sickle protein at all), and another 20% of cells had monoallelic editing (with one sickle allele and one corrected allele, conferring a level of protection expected to be similar to patients with “sickle cell trait” who do not show significant symptoms of disease). On a combined basis, we observed up to 93% of cells with potential elimination of sickle cell disease. Further, the correction of the HbS protein to the HbG-Makassar variant was shown to significantly reduce the propensity of *in vitro* differentiated erythroid cells to sickle when subjected to hypoxia. These findings represent therapeutic levels of correction if translated into clinic trials and support advancement of this program to potentially address the underlying genetic cause of sickle cell disease.

Long-term *in vivo* data generated using an early version of the Makassar base editor yielded approximately 50% conversion of the sickle allele to a Makassar allele. At 16 weeks post-transplant of CD34+ cells containing the sickle trait, we observed equivalent human chimerism between unedited and edited cells and evidence of multi-lineage reconstitution in mouse models. Levels of editing were sustained after long-term hematopoietic engraftment. Further, editing of the sickle allele led to the expression of the Makassar globin protein *in vivo*.

In December 2021, we presented data from preclinical studies further characterizing the Makassar hemoglobin created by BEAM-102 and demonstrating biophysical and biochemical properties consistent with normal hemoglobin. In these preclinical studies:

- BEAM-102 Makassar globin did not polymerize *in vitro*;
- Cells co-expressing BEAM-102 Makassar globin and sickle globin had properties similar to sickle trait cells, which are cells with one normal globin gene and one sickle globin gene and which do not sickle;
- Oxygen binding of BEAM-102 Makassar globin was comparable to the most abundant normal adult hemoglobin (HbA); and
- The crystal structures of BEAM-102 Makassar globin and of HbA were superimposable, suggesting no meaningful structural differences.

Published third party modeling studies suggest that at least 20% of cells no longer having the propensity to sickle, either by expressing HbF or because of the elimination of HbS, may be sufficient to cure sickle cell disease. With upregulation levels of more than 60% of gamma globin in the case of BEAM-101 or by generating more than 90% of cells having at least one HbS allele corrected in the case of BEAM-102, we have shown, in preclinical models, correction levels significantly above those expected to be disease modifying.

### **Wave 2: Improved Conditioning**

In parallel with Wave 1 development, we also aim to improve the transplant conditioning regimen for sickle cell disease patients undergoing HSCT, reducing toxicity challenges associated with HSCT standard of care. Conditioning is a critical component necessary to prepare a patient’s body to receive the *ex vivo* edited cells that must engraft in the patient’s bone marrow in order to be effective. Today’s conditioning regimens rely on nonspecific chemotherapy or radiation, which are associated with significant toxicities. We are collaborating with Magenta Therapeutics, Inc., or Magenta, to evaluate the potential utility of MGTA-117, Magenta’s novel antibody drug conjugate, in combination with BEAM-101 and BEAM-102, as well as other base editing programs in hematology. MGTA-117 is designed to spare immune cells and precisely target HSPCs, and has demonstrated high selectivity, potent efficacy, wide safety margins and broad tolerability in NHP models. We are also conducting our own research into novel conditioning strategies. Improved conditioning regimens could potentially be paired with BEAM-101 and BEAM-102, as well as other base editing programs in hematology.

### Wave 3: In Vivo Base Editing via HSC-targeted LNPs

We are also exploring the potential for *in vivo* base editing programs for sickle cell disease, in which base editors would be delivered to the patient through an infusion of LNPs targeted to HSCs, eliminating the need for transplantation altogether. This approach could provide a more accessible option for patients, particularly in regions where *ex vivo* treatment is challenging. Building on our acquisition of Guide, we are using our proprietary DNA-barcoded LNP screening technology to enable high-throughput *in vivo* identification of LNPs with novel biodistribution and selectivity for target organs beyond the liver. In December 2021, we announced we had screened more than 1,000 LNPs using this technology for potential to deliver to HSCs and had identified LNP-HSC1 as the most potent, with efficient transfection in both mice and NHPs. In preclinical studies, we demonstrated that:

- LNP-HSC1 was validated *in vivo*, leading to durable, dose-dependent mRNA transfection in HSCs and resulting in fluorescent reporter expression in more than 40% of cells, maintained out to 16 weeks post-delivery;
- LNP-HSC1 efficiently transfected human CD34+ cells *in vitro*; and
- LNP-HSC1 efficiently transfected nearly 20% of CD34+ HSCs in humanized mice and NHPs at a dose of 1.0 mg/kg.

### Ex vivo T cell therapies

The starting material for our multiplex-edited allogeneic CAR-T cell products is white blood cells from a healthy donor, which are collected using a standard blood bank procedure known as leukapheresis. Using a single electroporation, we introduce the base editor as mRNA, and the guides encoding the target sequences. The edited cells are subsequently transduced with a lentivirus expressing the CAR. Once the T cells have been engineered, they are expanded and frozen. After the patient is lymphodepleted, the multiplex-edited, allogenic cell product is infused.

We believe base editing is a powerful tool to simultaneously multiplex edit many genes without the unintended on-target effects that can result from simultaneous editing with nucleases through the creation of double-stranded breaks. The ability to create a large number of multiplex edits in T cells could endow CAR-T cells and other cell therapies with combinations of features that have the potential to dramatically enhance their therapeutic potential in treating hematological or solid tumors. The initial indications that we plan to target with these product candidates are relapsed, refractory T-ALL/T-LL, and Acute Myeloid Leukemia, or AML. We believe that our approach has the potential to produce higher response rates and deeper remissions than existing approaches. Our proof-of-concept preclinical studies have demonstrated the ability of base editors to efficiently modify up to eight genomic loci simultaneously in primary human T cells with efficiencies ranging from 85-95% as measured by flow cytometry of target protein knockdown. Importantly, these results have been achieved without the generation of observed chromosomal rearrangements, as evaluated by sensitive methods such as UDiTaS<sup>TM</sup> or G-banded Karyotyping and with no observed loss of cell viability from editing. The proof-of-concept preclinical studies have also demonstrated robust T cell killing of target tumor cells both *in vitro* and *in vivo*. We plan to nominate a second CAR-T development candidate, in addition to BEAM-201, in 2022.

### BEAM-201: Universal CD7-targeting CAR-T cells

BEAM-201 is a development candidate comprised of T cells derived from healthy donors that are simultaneously edited at *TRAC*, *CD7*, *CD52* and *PDCD1* and then transduced with a lentivirus encoding for an anti-CD7 CAR that is designed to create allogenic CD7 targeting CAR-T cells, resistant to both fratricide and immunosuppression. To our knowledge, BEAM-201 is the first investigational cell therapy featuring four simultaneous edits. We have initiated IND-enabling studies for BEAM-201 and expect to submit an IND to the FDA for the treatment of relapsed, refractory T-ALL/T-LL and potentially other CD7+ malignancies during the second half of 2022.

In our BEAM-201 program, we edit cells using our CBEs with the aim of conferring the following benefits:

- *TRAC*: Prevent graft-vs-host disease via the elimination of the existing TCR to ensure that the CAR-T cell only attacks the CAR antigen on the tumor and not the patient's healthy cells.
- *CD52*: Enable an allogeneic cell source by masking BEAM-201 cells to anti-CD52 lymphodepleting agents to reduce host rejection of BEAM-201 cells.
- *PDCD1*: Minimize immunosuppression of BEAM-201 cells by the tumor microenvironment and prolong efficacy for attacking the tumor.
- *CD7*: Prevent fratricide by eliminating antigens that are shared between malignant cells and CAR-T cells.

#### *Preclinical in vitro characterization of BEAM-201 and comparison to nuclease editing:*

- Simultaneous base editing at four target loci in primary human T cells using a clinical-scale process demonstrated 96-99% on-target editing of each of the four genes as measured by next-generation sequencing.
- Simultaneous quad base editing of T cells resulted in no detected genomic rearrangements; Cas9 nuclease editing with the same four guide RNAs produced chromosomal aberrations in 22 of 100 cells evaluated in G-banded karyotyping.
- Multiplex base editing did not demonstrate negative effects on cell expansion during manufacturing, while nuclease editing was observed to induce significant loss of cell expansion.
- CBE-edited cells demonstrated decreased expression of the four target genes with minimal effect on other genes, including key members of the p53 pathway that are upregulated in response to DNA double-stranded breaks produced by multiplex editing with nucleases.

#### *Further preclinical characterization of BEAM-201 in vitro and in a tumor mouse model:*

- The GMP-compliant, clinical-scale process resulted in final BEAM-201 CAR-T cell populations with on-target editing efficiencies between 96-99.9% at each of the four target loci, and 85% CAR-expressing cells. As a result, we estimate that 91% of cells are bi-allelically quad base edited and 77% of cells have all five genetic modifications. We believe this is the highest level and uniformity of CAR expression and simultaneous editing across four target sites reported at clinical scale to date.
- BEAM-201 cells demonstrated robust *in vitro* CD7-dependent cytokine production, and rapid *in vitro* cytotoxicity.
- BEAM-201 cells also demonstrated dose-dependent clearance or control, across a 25-fold dose range, of an aggressive disseminated CCRF-CEM T-ALL tumor mouse model.

#### **CD5-targeting CAR-T cells**

In October 2021, we announced preclinical data from our multiplex edited allogeneic CAR-T research program targeting CD5-positive hematologic malignancies. These data demonstrated knockout of CD5 expression to be a general mechanism to enhance potency and potentially improve durability of highly multiplexed CAR-T cells.

#### **In vivo LNP**

LNPs are a clinically validated technology for delivery of nucleic acid payloads to the liver. LNPs are multi-component particles that encapsulate the base editor mRNA and one or more guides and protect them from degradation while in an external environment, enabling the transient delivery of the base editor *in vivo*. Multiple third-party clinical trials have demonstrated the effective delivery of silencing RNA to the liver using LNPs. Because only one dose of a base editing therapy may be needed in a course of treatment, LNPs are a suitable delivery modality that we believe is unlikely to face the complications seen with chronic use of LNPs, such as those observed when delivering oligonucleotides or mRNA for gene therapy. All of the components of the LNP, as well as the mRNA encoding the base editor, are well-defined and can be manufactured synthetically, providing the opportunity for scalable manufacturing.

We have developed several proprietary LNP formulations. In May 2021, we announced initial data from our evaluation of various LNP formulations and mRNA production processes using an mRNA-encoding ABE and guide RNA to target the ALAS1 gene, a surrogate payload for genetic liver diseases. These data showed improved *in vivo* editing in the livers of NHPs from less than 10% initially to 52% at a total RNA dose of 1.5 mg/kg. Continued optimization of our LNP formulations has demonstrated further increases in liver editing potency in NHPs. In September 2021, we presented data demonstrating up to 60% editing in NHPs at a total RNA dose of 1.0 mg/kg. Data from our preclinical studies demonstrated that these formulations were well tolerated by NHPs treated with doses up to 1.5 mg/kg. Minimal to mild and transient liver enzyme elevations were observed and resolved by day 15 post-treatment. Additionally, the formulations showed promising interim stability, maintaining potency after three months at -20°C and -80°C.

We are currently using LNP formulations to advance our programs for genetic liver diseases, including GSDIa, also known as Von Gierke disease, and Alpha-1 Antitrypsin Deficiency, or Alpha-1. In December 2021, we nominated BEAM-301, a liver-targeting LNP formulation of base editing reagents designed to correct the R83C mutation, the most common disease-causing mutation of GSDIa, as our first *in vivo* development candidate. We anticipate initiating IND-enabling studies for BEAM-301 and nominating a second liver-targeted development candidate in 2022.

#### **Liver diseases: glycogen storage disorder 1a, alpha-1 antitrypsin deficiency and chronic hepatitis B infection**

##### **GSDIa**

GSDIa is an inborn disorder of glucose metabolism caused by mutations in the G6PC gene, which results in low blood glucose levels that can be fatal if patients do not adhere to a strict regimen of slow-release forms of glucose, administered every one to four hours (including overnight). There are no disease-modifying therapies available for patients with GSDIa.



Our approach to treating patients with GSDIa is to apply base editing via LNP delivery to repair the two most prevalent mutations that cause the disease, R83C and Q347X. It is estimated that these two point mutations account for 900 and 500 patients, respectively, in the United States, representing approximately 59% of all GSDIa patients in the United States. Third party animal studies have shown that as little as 11% of normal G6Pase activity in liver cells is sufficient to restore fasting glucose; however, this level must be maintained in order to preserve glucose control and alleviate other serious, and potentially fatal, GSDIa sequelae.

In October 2021, we reported data from preclinical studies that support the potential of base editing to durably correct disease-causing mutations of GSDIa. We created a novel, humanized R83C knockout mouse model (huR83C), mimicking the abnormal metabolic phenotype of human GSDIa, and collaborated with the National Institutes of Health, or NIH, to characterize the phenotype of these animals. The results demonstrated that newborn huR83C mice treated with our LNP-delivered ABE exhibited normal growth to the end of the study at three weeks of age without any hypoglycemia-induced seizures. In contrast, homozygous animals were unable to survive soon after birth in the absence of glucose supplementation. In addition, we observed editing efficiencies up to approximately 60% by next-generation sequencing of DNA isolated from the whole liver. Of note, we believe even narrow gains in base editing efficiency have the potential to provide significant restoration of G6Pase activity and normal metabolic function.

The findings presented in October 2021 were consistent with the results from prior preclinical models, which have shown up to 80% correction of the alleles in cells harboring the Q347X point mutation and approximately 60% of the alleles in cells harboring the R83C mutation. Significant, potentially disease-modifying levels of *in vivo* correction of both mutations by ABEs was observed in the livers of two strains of transgenic mice, each carrying one of the two relevant G6PC mutations. Next-generation sequencing data from whole liver extracts revealed approximately 40% and 70% A-to-G correction of R83C and Q347X, respectively. These significant levels of mutation correction observed greatly surpass those expected to restore glucose homeostasis, and functional preclinical studies are ongoing to correlate pathophysiology to the extent of mutation correction by base editing. Further, these levels of *in vivo* correction for GSDIa by base editing were achieved without the creation of double-stranded breaks. In total, these data support base editing technology as a promising approach for precise correction of two of the most prevalent causative mutations in GSDIa.

### *Alpha-1*

Alpha-1 is a severe inherited genetic disorder that can cause progressive lung and liver disease. The most severe form of Alpha-1 arises when a patient has a point mutation in both copies of the SERPINA1 gene at amino acid 342 position (E342K, also known as the PiZ mutation or the “Z” allele). This point mutation causes Alpha-1 antitrypsin, or AAT, to misfold, accumulating inside liver cells rather than being secreted, resulting in very low levels (10%-15%) of circulating AAT. As a consequence, the lung is left unprotected from neutrophil elastase, resulting in progressive, destructive changes in the lung, such as emphysema, which can result in the need for lung transplants. The mutant AAT protein also accumulates in the liver, causing liver inflammation and cirrhosis, which can ultimately cause liver failure or cancer requiring patients to undergo a liver transplant. It is estimated that approximately 60,000 individuals in the United States have two copies of the Z allele. There are currently no curative treatments for patients with Alpha-1.

With the high efficiency and precision of our base editors, we aim to utilize our ABEs to precisely correct the E342K point mutation back to the wild type sequence.

In a preclinical study, we engineered novel ABEs and guide RNAs capable of correcting the PiZ mutation, and then used a proprietary non-viral LNP formulation to deliver the optimized reagents to the livers of a PiZ transgenic mouse model. This direct editing approach resulted in an average of 16.9% correction of beneficial alleles at seven days and 28.8% at three months. This significant increase over the period suggests that corrected hepatocytes may have a survival advantage relative to uncorrected cells. In addition, treated mice demonstrate decreased Alpha-1-antitrypsin-mediated globule burden within the liver and a durable, significant increase in serum AAT active protein at three months, approximately 4.9-fold higher than in controls at the end of the study, levels which we believe would be clinically relevant if achieved in clinical trials. These data indicate the potential for base editing as a one-time therapy to treat both lung and liver manifestations of Alpha-1.

### *Hepatitis B Virus*

Hepatitis B virus, or HBV, causes serious liver infection that can become chronic, increasing the risk of developing life-threatening health issues like cirrhosis, liver failure or liver cancer. Chronic HBV infection is characterized by the persistence of covalently closed circular DNA, or cccDNA, a unique DNA structure that forms in response to HBV infection in the nuclei of liver cells. Additionally, the HBV DNA can integrate into the human genome becoming a source of hepatitis B surface antigen, or HBsAg. While currently available treatments can manage HBV replication, they do not clear cccDNA from the infected liver cells. This inability to prevent HBV infection rebound from cccDNA is a key challenge to curing HBV. In September 2021, we presented preclinical data that demonstrated the potential of our CBEs to reduce viral markers, including HBsAg expression, and prevent viral rebound of HBV in *in vitro* models.

## ***In vivo AAV***

AAV is a clinically validated technology that has been extensively used for gene delivery to a variety of tissues. AAV is a small, non-pathogenic virus that can be repurposed to carry a therapeutic payload, making it a suitable vector for delivery of gene editing therapies. Several clinical trials have been conducted or are in progress with different AAV variants for multiple diseases, including diseases of the eye, liver, muscle, lung and central nervous system. We have an option to in-license a variety of AAV variants that could be selected for optimal distribution to multiple organs. Because our DNA base editors are larger than the approximate 4.5kb packaging limit of AAV vectors, we use a novel split intein technology that is designed to deliver the base editor and guide RNA by co-infection with two viruses, where each virus contains approximately one half of the editor.

### ***Ocular disorders: Stargardt disease***

We are currently evaluating this technology to correct one of the most prevalent mutations in the ABCA4 gene causing Stargardt disease, a progressive macular degeneration disease. This mutation is known as the G1961E point mutation and approximately 5,500 individuals in the United States are affected. Disease modeling using tiny light stimuli through holes that are equivalent in size to a single photoreceptor cell suggests that only 12%-20% of these cells are necessary to preserve vision. We anticipate, therefore, that editing percentages in the range of 12%-20% of these cells would be disease-modifying, since each edited cell will be fully corrected and protected from the biochemical defect associated with Stargardt disease.

In a human retinal pigment epithelial cell line (ARPE-19 cells) in which we have knocked in the ABCA4 G1961E point mutation, we have demonstrated the precise correction of approximately 75% of the disease alleles at five weeks after dual infection with the split AAV system. In November 2021, we announced that we have initiated preclinical studies in NHPs for our Stargardt program.

### ***Our portfolio of precision gene editing technologies***

Building on the expertise of our academic founders and our innovative research culture, we plan to explore new and complementary technologies in base editing, gene editing, and genetic medicine over the long term to advance a broad portfolio across multiple delivery pipelines. As part of this strategy, we have licensed a portfolio of three additional complementary technologies – RNA base editing, Cas12b nuclease editing, and prime editing for certain fields. Combined with base editing, we have assembled a broad and versatile portfolio of next generation gene editing technologies for the potential treatment of many severe diseases.

Our license agreement with The Broad Institute, Inc., or Broad Institute, gives us access to RNA base editing technology, a two-part modular system using an RNA-directed CRISPR protein for targeting RNA strands and a deaminase for editing. This CRISPR protein, known as Cas13, is modified so that it cannot break the RNA strand, and is fused to a deaminase capable of making a single base edit at a specific target location within the RNA strand. This enables us to change protein expression, potentially correcting or altering the function of the resulting protein and correcting disease. Our RNA base editing technologies include the REPAIR™ system for A-to-I editing, as well as the RESCUE™ system for C-to-U editing. When delivered through a long-lasting viral vector, RNA base editing may provide a complementary approach to DNA base editing for permanent correction of gene expression. Additionally, RNA editing could potentially be beneficial in situations where a transient change is desirable, such as in regenerative medicine.

Our Broad Institute license also gives us access to the Cas12b nuclease family, which provides several potential strategic advantages for our portfolio. First, the distinct PAM sequence and conformation of Cas12b allows us to create DNA base editors that can bind to different target sites in the genome, further expanding the range of sites that we can edit. Second, having a nuclease allows us to make “cut” edits, which may be appropriate for some applications that require a double stranded break, or to use the general gene targeting ability of Cas12b for other gene editing applications.

We also have a license to technology referred to as “prime editing,” that is controlled by Prime Medicine, Inc. Prime editing may be able to achieve the “rewriting” of short sequences of DNA at a target location. Prime editing utilizes a CRISPR protein to target a mutation site in DNA and to nick a single strand of the target DNA. The guide RNA allows the CRISPR protein to recognize a DNA sequence that is complementary to the guide RNA and also carries a primer for reverse transcription and a replacement template. The reverse transcriptase copies the template sequence in the nicked site, installing the edit. As with base editing, prime editing does not cause double-stranded breaks in the target DNA, resulting in lower insertion and deletion rates than gene editing technologies that rely on double stranded breaks.

We have the exclusive right to develop prime editing technology for the creation or modification of any single base transition mutations, as well as any edits made for the treatment of sickle cell disease. Transition mutations (i.e., A-to-G, G-to-A, C-to-T, or T-to-C) are the largest single class of disease-associated genetic mutations and include all of our current targets for base editing programs.

Leveraging our deep scientific expertise and significant ongoing investment in our platform, we also expect to develop insights into other innovative gene editing and delivery modalities. We believe that our delivery, manufacturing, and development capabilities could position us to effectively evaluate and rapidly develop such novel technologies and further extend our leadership in the field of genetic medicine.

## Collaborations

We believe our collection of base editing, gene editing and delivery technologies has significant potential across a broad array of genetic diseases. To fully realize this potential, we have established and will continue to seek out innovative collaborations, licenses, and strategic alliances with pioneering companies and with leading academic and research institutions. Additionally, we have and will continue to pursue relationships that potentially allow us to accelerate our preclinical research and development efforts. These relationships will allow us to aggressively pursue our vision of maximizing the potential of base editing to provide life-long cures for patients suffering from serious diseases.

### *In vivo collaborations*

#### *Pfizer*

In December 2021, we entered into a four-year research collaboration agreement with Pfizer Inc., or Pfizer, focused on *in vivo* base editing programs for three targets for rare genetic diseases of the liver, muscle and central nervous system. Under the terms of the agreement, we will conduct all research activities through development candidate selection for three pre-specified, undisclosed targets, which are not included in our existing programs. Pfizer may opt in to exclusive, worldwide licenses to each development candidate, after which it will be responsible for all development activities, as well as potential regulatory approvals and commercialization, for each such development candidate. We have a right to opt in, at the end of Phase 1/2 clinical trials, upon the payment of an option exercise fee, to a global co-development and co-commercialization agreement with respect to one program licensed under the collaboration pursuant to which we and Pfizer would share net profits as well as development and commercialization costs in a 35%/65% ratio (Beam/Pfizer).

#### *Apellis Pharmaceuticals*

In June 2021, we entered into a research collaboration agreement with Apellis Pharmaceuticals, Inc., or Apellis, focused on the use of certain of our base editing technology to discover new treatments for complement system-driven diseases. Under the terms of the agreement, we will conduct preclinical research on up to six base editing programs that target specific genes within the complement system in various organs, including the eye, liver, and brain. Apellis has an exclusive option to license any or all of the six programs and will assume responsibility for subsequent development. We may elect to enter into a 50-50 U.S. co-development and co-commercialization agreement with Apellis with respect to one program licensed under the collaboration.

#### *Verve Therapeutics*

In April 2019, we entered into a collaboration and license agreement, or the Verve Agreement, with Verve Therapeutics, Inc., or Verve, a company focused on gene editing for cardiovascular disease treatments. This collaboration allows us to more fully realize the potential of base editing in treating cardiovascular disease, a disease area outside of our core focus and where Verve has significant expertise. Under the terms of the Verve Agreement, Verve received exclusive worldwide licenses to use our base editing technology and certain gene editing and delivery technologies for human therapeutic applications against certain cardiovascular targets. In exchange, we received shares of Verve common stock. Additionally, we are eligible to receive milestone payments for certain clinical and regulatory events for licensed products, and we retain the option, after the completion of Phase 1 clinical trials, to participate in future development and commercialization, and share 50 percent of U.S. profits and losses, for any licensed product directed against these targets.

In January 2021, Verve announced it had selected VERVE-101 as its lead product to be developed initially for the treatment of heterozygous familial hypercholesterolemia, or HeFH, a potentially fatal genetic heart disease. Individuals with HeFH have a genetic mutation causing high LDL-C levels in the blood. Over time, high LDL-C builds up in the heart's arteries, resulting in reduced blood flow or blockage, and ultimately heart attack or stroke. Inactivation of the proprotein convertase subtilisin/kexin type 9, or PCSK9, gene has been shown to up-regulate LDL receptor expression, which leads to lower LDL-C levels. By making a single A-to-G change in the DNA genetic sequence of PCSK9, VERVE-101 aims to inactivate the target gene. In January 2021, Verve also reported preclinical proof-of-concept data in NHPs that demonstrated the successful use of ABEs to turn off PCSK9, and in January 2022, Verve announced it expects to submit an IND application for VERVE-101 in the second half of 2022.

#### *Institute of Molecular and Clinical Ophthalmology Basel*

In July 2020, we announced a research collaboration with the Institute of Molecular and Clinical Ophthalmology Basel, or IOB. Founded in 2018 by a consortium that includes Novartis, the University Hospital of Basel and the University of Basel, IOB is a leader in basic and translational research aimed at treating impaired vision and blindness. Clinical scientists at IOB have also helped to develop better ways to measure how vision is impacted by Stargardt disease.

Additionally, researchers at IOB have developed living models of the retina, known as organoids, which can be used to test novel therapies. Under the terms of the agreement with IOB, the parties will leverage IOB's unique expertise in the field of ophthalmology along with our novel base editing technology to advance programs directed to the treatment of certain ocular diseases, including Stargardt disease.

## **Ex vivo collaborations**

### *Sana Biotechnology*

In October 2021, we entered into an option and license agreement, or the Sana Agreement, with Sana Biotechnology, Inc., or Sana, pursuant to which we granted Sana non-exclusive research and development and commercial rights to our CRISPR Cas12b technology to perform nuclease editing for certain *ex vivo* engineered cell therapy programs. Under the terms of the Sana Agreement, licensed products include certain specified allogeneic T cell and stem cell-derived products directed at specified genetic targets, with certain limited rights for Sana to add and substitute such products and targets. The Sana Agreement excludes the grant of any Beam-controlled rights to perform base editing.

### *Boston Children's Hospital*

In July 2020, we entered into an alliance agreement, or the BCH Agreement, with Boston Children's Hospital, or Boston Children's. Under the terms of the BCH Agreement, we will identify and sponsor research programs to be performed at Boston Children's either solely by Boston Children's or by both Boston Children's and us, to facilitate the development of certain disease-specific therapies using our proprietary base editing technology. Boston Children's will also serve as a clinical site to advance bench-to-bedside translation of our pipeline across certain therapeutic areas of interest, including programs in sickle cell disease and pediatric leukemias and exploration of new programs targeting other diseases.

### *Magenta Therapeutics*

In June 2020, we announced a non-exclusive research and clinical trial collaboration agreement with Magenta Therapeutics Inc., or Magenta, to evaluate the potential utility of MGTA-117, Magenta's novel targeted antibody-drug conjugate, for conditioning of patients with sickle cell disease and beta-thalassemia receiving our base editing therapies. Conditioning is a critical component necessary to prepare a patient's body to receive the edited cells, which carry the corrected gene and must engraft in the patient's bone marrow in order to be effective. Today's conditioning regimens rely on nonspecific chemotherapy or radiation, which are associated with significant toxicities. MGTA-117 is designed to precisely target only hematopoietic stem and progenitor cells, to spare immune cells, and has shown high selectivity, potent efficacy, wide safety margins and broad tolerability in non-human primate models. MGTA-117 may be capable of clearing space in bone marrow to support long-term engraftment and rapid recovery in patients. Combining the precision of our base editing technology with the more targeted conditioning regimen enabled by MGTA-117 has the potential to further improve therapeutic outcomes for patients suffering from these severe diseases.

## **Competition**

The pharmaceutical and biotechnology industries, including the gene editing field, are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on intellectual property. While we believe that our differentiated technology, scientific expertise, and intellectual property position provide us with competitive advantages, we face potential competition from a variety of companies in these fields. Within these industries, we will compete with existing large pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies.

There are several other companies utilizing CRISPR/Cas9 nuclease technology, including Caribou Biosciences, Editas Medicine, CRISPR Therapeutics, Intellia Therapeutics, Arbor Biotechnologies, Metagenomi, and Mammoth Biosciences. Several additional companies utilize other nuclease-based gene editing technologies, including Zinc Fingers, Arcuses, and TAL Nucleases, including Sangamo Biosciences, Precision BioSciences, bluebird bio, Allogene Therapeutics and Collectis. Additionally, newer gene editing modalities are emerging, including from Prime Medicine, Tessera Therapeutics, Shape Therapeutics, Scribe Therapeutics, Korro Bio, PerkinElmer (formerly Horizon Discovery) and Intellia Therapeutics. PerkinElmer and Intellia Therapeutics are developing base editing technology and Tessera Therapeutics is utilizing mobile genetic elements for gene editing. In addition, we face competition from companies utilizing various gene therapy, oligonucleotides, and CAR-T therapeutic approaches.

We are also aware of companies with products in development in our disease areas where we will compete with approved therapies, those in development today, and those emerging in the future. For hemoglobinopathies, these companies include Global Blood Therapeutics, CRISPR Therapeutics, Novartis Pharmaceuticals, Sangamo Therapeutics, Editas Medicine, Homology Medicines, Graphite Bio and Vera Therapeutics (formerly TruCode Gene Repair). For T-cell malignancies, these include Gracell Bio, iCell Gene Therapeutics, PersonGen and Wugen. More broadly in the immuno-oncology cell therapy space, these include Allogene Therapeutics, Collectis, 2seventy bio, Bristol Myers Squibb, Fate Therapeutics, Gilead Sciences, Novartis Pharmaceuticals, Poseida Therapeutics, Precision Bio, Legend Biotech and Autolus Therapeutics. For our liver targeted therapies, these include Intellia Therapeutics, Editas Medicines, CRISPR Therapeutics, Ultragenyx, Apic Bio, Arrowhead Pharmaceuticals, LogicBio Therapeutics, Generation Bio and Vertex.

Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future that are approved to treat the same diseases for which we may obtain approval for our product candidates. This may include other types of therapies, such as small molecule, antibody, and/or protein therapies.

In addition, many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, conducting preclinical studies and clinical trials and seeking approval for products than we do today. Mergers and acquisitions in the pharmaceutical, biotechnology and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. We also compete with these companies in recruiting, hiring and retaining qualified scientific and management talent, establishing clinical trial sites and patient registration for clinical trials, obtaining manufacturing slots at CMOs, and in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, particularly if they represent cures, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop. Our competitors also may obtain 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. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety, convenience, and availability of reimbursement.

### **Intellectual property**

Our success depends in part on our ability to obtain and maintain proprietary protection for our platform technology, our programs, and know-how related to our business, defend and enforce our intellectual property rights, in particular, our patent rights, preserve the confidentiality of our trade secrets, and operate without infringing, misappropriating or otherwise violating any valid and enforceable intellectual property rights of others. We seek to protect our proprietary position by, among other things, exclusively licensing and filing U.S. and certain foreign patent applications related to our platform technology, existing and planned programs, and improvements that are important to the development of our business, where patent protection is available. Notwithstanding these efforts, we cannot be sure that patents will be granted with respect to any patent applications we have licensed or filed or may license or file in the future, and we cannot be sure that any patents we have licensed or patents that may be licensed or granted to us in the future will not be challenged, invalidated, or circumvented or that such patents will be commercially useful in protecting our technology. For more information regarding the risks related to our intellectual property, please see Item 1A., *Risk factors—Risks related to our intellectual property*, in this Annual Report on Form 10-K.

Our wholly owned and our in-licensed patents and patent applications cover various aspects of our base editing platform and our programs, including:

- C-to-T DNA base editors
- A-to-G DNA base editors
- A-to-I RNA base editors, or REPAIR
- C-to-U RNA base editors, or RESCUE
- CRISPR/Cas12b systems for nuclease editing
- Novel guide RNA sequences
- Systems and methods for increasing the specificity of base editing
- Multiplex base editing in immune cells *ex vivo*
- Methods for evaluating base editing specificity
- Therapeutic methods
- Delivery modality

We also have an option to license patents and patent applications relating to CRISPR/Cas9 systems. We intend to continue to pursue, when possible, additional patent protection, including composition of matter, method of use, and process claims, directed to each component of our platform technology and the programs in our portfolio. We also intend to obtain rights to delivery modalities through one or more licenses from third parties and to protect our own intellectual property to delivery modalities.

As of December 31, 2021, we owned approximately two U.S. patents, 42 pending U.S. provisional patent applications, 24 pending U.S. patent applications, 14 pending international patent applications, or PCT applications, and 128 pending ex-U.S. patent applications. The patent applications outside of the United States were filed in Australia, Brazil, Canada, China, Europe, Hong Kong, India, Japan, Korea, Singapore and South Africa. Our owned patent applications are related to our DNA base editing technology, as further described below, including claims to base editor variants with enhanced activities (e.g., nucleobase deaminating activity) or novel properties (e.g., PAM recognition), methods of using such base editors, methods of using such base editors for therapeutic indications, multiplex base editing in immune cells *ex vivo*, guide RNAs that target base editors to therapeutically relevant DNA sequences, and methods for evaluating base editing specificity. Some aspects of our owned patent applications are related to viral and non-viral delivery technologies, as further detailed below. One of the PCT applications is co-owned with Broad Institute and President and Fellows of Harvard College, or Harvard. If issued as U.S. patents, and if the appropriate maintenance fees are paid, the U.S. patents would be expected to expire between 2039 and 2043, excluding any additional term for patent term adjustments or patent term extensions.

#### **DNA base editing**

Beam's owned portfolio includes approximately two U.S. patents, 21 pending U.S. patent applications, 13 pending U.S. provisional patent applications, 116 pending ex-U.S. patent applications and five pending PCT applications directed to DNA base editing. As of December 31, 2021, we in-licensed approximately 11 U.S. patents, 16 pending U.S. patent applications, 30 ex-U.S. patents, and 96 pending ex-U.S. patent applications, related to DNA base editing from Broad Institute, Harvard, Editas Medicine Inc., or Editas, and Bio Palette Co., Ltd., or Bio Palette. The patents and patent applications outside of the United States were filed in jurisdictions including Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan and Korea. The patents and applications from our in-licensed portfolio for DNA base editing include claims to novel base editors, claims to engineered deaminase enzymes (e.g., evolved Tada) used in the base editors, compositions including the base editor or engineered deaminase as a component, methods of using such base editors, including methods of using such base editors for therapeutic indications, guide RNAs that target base editors to therapeutically relevant DNA sequences. The in-licensed patents and applications also cover various aspects related to the platform technology, including base editing systems that employ *S. pyogenes* Cas9, *S. aureus* Cas9, Cas9 PAM variants, inactive forms of Cas9, and/or Cas9 nickases, and systems for delivery of base editors. Our current in-licensed patents and patent applications on DNA base editing, if the appropriate maintenance fees are paid, are expected to expire between 2034 and 2038, excluding any additional term for patent term adjustments or patent term extensions (or the corresponding foreign equivalent).

#### **RNA Base Editing**

As of December 31, 2021, we in-licensed approximately one U.S. patent, 17 pending U.S. patent applications, five ex-U.S. patents, and 66 pending ex-U.S. patent applications, related to RNA base editing from Broad Institute. The patents and patent applications outside of the United States were filed in jurisdictions including Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea and Russia. The patents and applications from our in-licensed portfolio for RNA base editing include claims to novel base editors, compositions including the base editor as a component, guide RNAs that target base editors to therapeutically relevant RNA sequences, and methods of using such base editors, including methods of using such base editors for therapeutic indications. Our current in-licensed patents and patent applications on RNA base editing, if the appropriate maintenance fees are paid, are expected to expire between 2036 and 2038, excluding any additional term for patent term adjustments or patent term extensions (or the corresponding foreign equivalent).

#### **CRISPR/Cas12b**

As of December 31, 2021, we in-licensed approximately one U.S. patent, six pending U.S. patent applications, and 15 pending ex-U.S. patent applications, related to editing using Cas12b from Broad Institute. The patents and patent applications outside of the United States were filed in jurisdictions including Australia, Canada, China, Europe, Hong Kong, Japan, Korea and Russia. The patents and applications from our in-licensed portfolio for Cas12b editing include claims to methods of using Cas12b to modify DNA (e.g., nuclease cleavage of DNA) and engineered and/or non-naturally occurring compositions including Cas12b as a component. Our current in-licensed patents and patent applications on Cas12b base editing, if the appropriate maintenance fees are paid, are expected to expire between 2036 and 2039, excluding any additional term for patent term adjustments or patent term extensions (or the corresponding foreign equivalent).

## ***Delivery technologies***

Beam's owned portfolio includes approximately four pending U.S. patent applications, 18 pending U.S. provisional patent applications, 11 pending ex-U.S. patent applications and five pending PCT applications directed to delivery technologies. As of December 31, 2021, we in-licensed approximately six U.S. patents, five pending U.S. patent applications, 11 ex-U.S. patents, 31 pending ex-U.S. patent applications and three pending PCT applications related to viral and non-viral based delivery technologies. The patents and patent applications outside of the United States were filed in jurisdictions including Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea, New Zealand and Singapore. The patents and applications from our in-licensed portfolio for delivery technologies include claims to novel lipid-based delivery systems and compositions, viral-based delivery systems and compositions, and methods of using such systems and compositions to deliver base editors. Our current in-licensed patents and patent applications on delivery technologies, if the appropriate maintenance fees are paid, are expected to expire between 2034 and 2040, excluding any additional term for patent term adjustments or patent term extensions (or the corresponding foreign equivalent).

## ***Rest of platform***

As of December 31, 2021, we in-licensed approximately 12 U.S. patents, eight pending U.S. patent applications, 22 ex-U.S. patents, and 26 pending ex-U.S. patent applications, related to the balance of our platform from universities and institutions. The patents and patent applications outside of the United States were filed in jurisdictions including Australia, Canada, China, Europe, Hong Kong, Japan, Korea and New Zealand. The patents and applications from our in-licensed portfolio for the balance of our platform include claims to compositions and methods for delivery of charged base editor proteins into cells, modification and improvements to the base editing systems including improvements to the nucleotide binding protein component, guide RNA component and base editing enzyme component of the base editing complex, methods for evaluating gene targeting and base editing efficiency and compositions and methods for prime editing. Our current in-licensed patents and patent applications on the balance of our platform, if the appropriate maintenance fees are paid, are expected to expire between 2034 and 2039, excluding any additional term for patent term adjustments or patent term extensions (or the corresponding foreign equivalent).

## ***CRISPR/Cas9 and CRISPR/Cas12a***

We have a nonexclusive license to conduct research activities and an option to exclusively license certain patents and patent applications directed to Cas9 and Cas12a from Editas, who in turn has licensed such patents from various academic institutions. In the case of Cas9, a number of the U.S. patents are subject to an interference declared by the Patent and Trademark office, and a number of the European patents are the subject of one or more oppositions. For more information regarding the risks related to our intellectual property, please see Item 1., *Business—Intellectual property—Intellectual property licenses* and Item 1A., *Risk factors—Risks related to our intellectual property*, in this Annual Report on Form 10-K.

The term of individual patents depends upon the legal term for patents in the countries in which they are granted. In most countries, including the United States, the patent term is 20 years from the earliest claimed filing date of a non-provisional patent application in the applicable country. However, the actual protection afforded by a patent varies from country to country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. In the United States, a patent's term may, in certain cases, be lengthened by patent term adjustment, or PTA, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened (e.g., if a patent is terminally disclaimed over a commonly owned patent having an earlier expiration date). In some instances, such a PTA may result in a U.S. patent term extending beyond 20 years from the earliest date of filing a non-provisional patent application related to the U.S. patent. Patent term extensions, or PTE, under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, are also possible for patents that cover an FDA-approved drug as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a PTE of up to five years beyond the expiration of the patent. The length of the PTE is related to the length of time the drug is under regulatory review. PTE cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug, a method for using it, or a method of manufacturing it, may be extended. Similar provisions are available in Europe and certain other jurisdictions to extend the term of a patent that covers an approved drug. In the future, if our products receive regulatory approval, we may be eligible to apply for PTEs on patents covering such products, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such PTE should be granted, and if granted, the length of such PTE. For more information regarding the risks related to our intellectual property, please see Item 1A., *Risk factors—Risks related to our Intellectual property*, in this Annual Report on Form 10-K.

We also rely on trade secrets, know-how, continuing technological innovation, and confidential information to develop and maintain our proprietary position and protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have implemented measures to protect and preserve our trade secrets, such measures can be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. For more information regarding the risks related to our intellectual property, please see Item 1A., *Risk factors—Risks related to our intellectual property*, in this Annual Report on Form 10-K.

### **Trademarks**

As of December 31, 2021, we owned approximately two pending U.S. trademarks applications with the Patent and Trademark Office for BEAM THERAPEUTICS and BEAM THERAPEUTICS and design, twelve ex-U.S. registered trademarks for BEAM THERAPEUTICS and BEAM THERAPEUTICS and design, and five ex-U.S. pending trademark applications for BEAM THERAPEUTICS and BEAM THERAPEUTICS and design.

As of December 31, 2021, we in-licensed approximately two pending U.S. trademarks, ten allowed/registered ex-U.S. trademarks, and seven pending ex-U.S. trademark applications, for the use of REPAIR™ and RESCUE™ from Broad Institute.

### **Intellectual property licenses**

We are a party to a number of license agreements under which we license patents, patent applications, and other intellectual property from third parties. The licensed intellectual property covers, in part, CRISPR-related compositions of matter and their use for base editing. 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 President and Fellows of Harvard College***

In June 2017, we entered into a license agreement with Harvard, as amended, or the Harvard License Agreement, pursuant to which we received an exclusive, worldwide, royalty-bearing, sublicensable license under certain patent rights owned or controlled by Harvard to make, have made, offer for sale, sell, have sold and import licensed products in the field of the prevention or treatment of any and all human diseases and conditions, excluding human germline modification and products for non-human animal and plant applications. We also received a non-exclusive, worldwide, royalty-bearing, sublicensable license to research, have researched, develop and have developed “enabled” products related to the Harvard patent rights which are not licensed products.

The licensed patents are directed, among other things, to C-to-T, A-to-G, and C-to-G base editors, for the treatment of certain diseases and conditions and to base editing, more generally.

Under the Harvard License Agreement, we are required to use commercially reasonable efforts to develop products incorporating the base editing technology covered in the licensed patents, in accordance with a development plan that we prepared and submitted to Harvard. The development plan includes certain development milestones that we are required to meet, as well as the timelines for the completion thereof, and we may update the development plan from time to time as we believe necessary, in our good faith judgment, for us to meet such milestones. If we are successfully able to gain regulatory approval in any country to introduce a licensed product into the commercial market in such country, then we are also required to use commercially reasonable efforts to commercialize such licensed product and make such licensed product reasonably available to the public. If we fail to meet any of the deadlines for the development milestones, then Harvard may, depending on the nature of the failure and the impacted milestones, either terminate the Harvard License Agreement or our licenses with respect to the applicable licensed product(s), subject to certain exceptions and opportunities for us to cure such failure. Additionally, we are required to initiate a discovery program in accordance with the development plan and development milestones for the development of a licensed product covered by certain sub-categories of licensed patents. Failure to achieve milestones with respect to such sub-categories gives Harvard the right to grant third parties non-exclusive licenses under such failed sub-categories.



The licenses granted to us under the Harvard License Agreement are expressly subject to certain preexisting rights held by Harvard and certain third parties. For example, certain of the licensed patents were developed by employees of the Howard Hughes Medical Institute and were subsequently assigned to Harvard but remain subject to a non-exclusive license between Harvard and Howard Hughes, pursuant to which Howard Hughes received a license from Harvard under certain of the licensed patents for research purposes with the right to sublicense to non-profit and governmental entities. In addition, certain of the licensed patents claim or cover inventions resulting from research that was sponsored by the U.S. government, and the U.S. government retains certain rights with respect to such licensed patents under applicable U.S. law. Harvard additionally retains limited rights for itself and for other non-profit research organizations to practice the licensed patents for research, educational, and scholarly purposes. Furthermore, Harvard retains the right, beginning a certain period of time after regulatory approval of any licensed product in the U.S. or certain European countries, to grant third parties the non-exclusive right to develop, manufacture, have manufactured, import, have imported, offer for sale, sell, have sold or otherwise distribute or have distributed such licensed product or an equivalent thereof solely for sale on a locally-affordable basis in certain specified developing countries in which we do not have plans to seek regulatory approval.

Although the licenses granted to us under the Harvard License Agreement are exclusive, Harvard may grant a license to a third party under the licensed patents to research, develop, and commercialize a product directed to one or more particular targets, or a proposed product, in the field under limited circumstances. If a third party that is not a specified competitor of ours inquires with Harvard for such a license, and then attempts to enter into a sublicense agreement with us after being referred to us by Harvard and fails to do so after a certain period of time and presents to Harvard a proposal including certain information describing the proposed development and commercialization of such product, then Harvard may notify us of such proposal. If we are not researching, developing or commercializing such a proposed product, then we can notify Harvard as to whether we are interested in developing such proposed product, entering into a sublicense agreement with such third party to develop such proposed product, or entering into a sublicense with another third party to develop the same proposed product. If we inform Harvard that we are interested in developing such proposed product, then we will prepare a development plan, similar in scope to the development plan under the Harvard License Agreement, to develop such proposed product. If we inform Harvard that we are interested in entering into a sublicense agreement pursuant to which a third party would receive a sublicense from us under the licensed patents to develop such proposed product, then we will have a specified period of time to enter into such a sublicense agreement and provide reasonable evidence thereof. If we are not researching, developing, or commercializing such a proposed product, fail to provide a development plan, or fail to enter into a sublicense agreement with respect to such proposed product, in each case, within specified time periods, then Harvard may grant a license to the applicable third party under the licensed patents to research, develop, and commercialize such proposed product.

We are permitted to further sublicense our rights under the Harvard License Agreement to third parties, provided that any such sublicense agreement with a third party must remain in compliance with and be consistent with the terms of the Harvard License Agreement, and certain rights granted to us under the Harvard License Agreement can only be sublicensed to *bona fide* collaboration partners who are working with us to develop one or more licensed products. In addition, any such sublicense agreement must include certain provisions to ensure our ability to comply with the Harvard License Agreement. We are also responsible for any breaches of a sublicense agreement by the applicable sublicensee, if such breach results in a material breach of the Harvard License Agreement, provided that if we cure the breach or diligently enforce our rights to terminate the sublicense, we will not be subject to termination by Harvard for the sublicensee's breach, even if it resulted in a material breach of the Harvard Agreement.

In exchange for the licenses granted to us under the Harvard License Agreement, we initially issued to Harvard 101,363 shares of our common stock and subsequently issued 765,549 shares of our common stock pursuant to anti-dilution rights in the Harvard License Agreement. We are also required to pay to Harvard an annual license maintenance fee ranging from low-to-mid five figures to low six figures, depending on the particular calendar year. Harvard is also entitled to receive potential clinical and regulatory milestones in the mid-to-high eight figure range. If we undergo a change of control during the term of the Harvard License Agreement, then certain of the milestone payments would be increased. We paid Harvard a total of \$9.0 million upon the completion of our Series A and Series B financings.

In May 2021, the first success payment measurement occurred and amounts due to Harvard were calculated to be \$15.0 million. We elected to make the payment in shares of our common stock and issued 174,825 shares of our common stock to settle this liability on June 10, 2021. We may additionally owe Harvard success payments of up to an additional \$90.0 million.

With respect to the sale of licensed products by us, our affiliates or our sublicensees, Harvard is entitled to receive low single digit royalties on net sales of licensed products until, on a country-by-country basis, the latest of the expiration of (i) the last to expire valid claim of a licensed patent covering the applicable licensed product, (ii) the period of exclusivity associated with such licensed product in such country or (iii) a certain number of years after the first commercial sale of such licensed product in such country. We are entitled to certain reductions and offsets on these royalties with respect to a licensed product in a given country and certain increases in the event we, our affiliates or sublicensees bring patent challenges relating to any licensed patents (subject to an ability to delay and/or avoid such increases by diligently seeking to terminate and/or terminating the sublicense that has taken the applicable action). If we sublicense our rights to develop or commercialize a licensed product under the Harvard License Agreement to a third party and we receive non-royalty sublicense income, then Harvard is entitled to a percentage of such consideration, ranging from the high single digits to an amount in the first decile depending on the date in which such sublicense agreement is executed and the stage of development our licensed products at such time.

Harvard is responsible for the prosecution and maintenance of all licensed patents, provided that we have customary consultation, comment, and review rights with respect to such prosecution and maintenance activities. We are responsible for Harvard's documented out-of-pocket expenses with respect to such prosecution and maintenance, but if Harvard enters into a license agreement with a third party pursuant to which it grants such third party a license under the licensed patents outside of our field, then Harvard must use reasonable efforts to include a provision in such agreement that provides for an apportionment of prosecution and maintenance costs between us and such third party with respect to such licensed patents. If we choose to no longer pay for the prosecution and maintenance costs of a given licensed patent, then we will be relieved of such payment obligation, but our license with respect to such licensed patent will also terminate.

Unless earlier terminated, the Harvard License Agreement will remain in effect until the later of the last-to-expire valid claim of the licensed patents or the end of the last to expire royalty term. We may terminate the Harvard License Agreement at our convenience following written notice to Harvard. Either party may terminate the Harvard License Agreement for a material breach of the other party, subject to a notice and cure period. Harvard may also terminate the Harvard License Agreement in the event of our bankruptcy or insolvency or if we fail to procure and maintain insurance. Upon expiration or termination of the Harvard License Agreement, the licenses granted to us will terminate and all rights under the licensed patent rights will revert to Harvard.

#### ***License Agreement with Editas Medicine, Inc.***

In May 2018, we entered into a license agreement, or the Editas License Agreement, with Editas pursuant to which we received an exclusive (even as to Editas), royalty-bearing, sublicensable, worldwide license under certain patent rights owned or controlled by Editas related to certain base editing technologies and CRISPR technology to develop, commercialize, make, have made, use, offer for sale, sell and import certain base editing products for the treatment of human diseases or conditions. The license we received is non-exclusive with respect to certain specified targets. Our licensed field excludes the treatment of certain diseases and certain fields of use that have already been licensed to other partners of Editas, provided that our licensed field may expand if the fields licensed to other Editas partners are reduced or are otherwise modified as a result of any termination, expiration, or amendment to Editas' agreements with such partners. In addition, we received a royalty-free, non-sublicensable, non-exclusive license under a separate set of patent rights owned or controlled by Editas to conduct research activities in our licensed field and for which we have an option to obtain an exclusive license from Editas.

Certain of the patents licensed to us under the Editas License Agreement were licensed to Editas from Broad Institute and Harvard and certain of the patents for which we have an option to obtain a license were licensed to Editas from the Massachusetts General Hospital, or MGH. Accordingly, the licenses granted to us under the Editas License Agreement are subject to the terms and conditions set forth in each of the license agreements concerning the licensed patents between Broad Institute, Harvard and Editas, or the Broad/Harvard Head Licenses, and each of the license agreements concerning the patents for which we have an option to obtain a license between MGH and Editas, or the MGH Head Licenses.

As described above, Editas granted us an exclusive option to obtain an exclusive license under certain patents on a patent family-by-patent family basis. If we so exercise the option with respect to a patent family of such optioned patents, then we would receive an exclusive license to such patent family of the same scope as the other patents exclusively licensed to us under the Editas License Agreement. In order to exercise an option with respect to a patent family of these optioned patents we would pay an eight-figure option exercise fee, depending on the date in which particular option is exercised.

Under the Editas License Agreement, we are required to use commercially reasonable efforts to develop a licensed product in our licensed field in each of the United States, Japan, the United Kingdom, or U.K., Germany, France, Italy and Spain, including filing the first IND for a licensed product within a certain period of time following the execution of the Editas License Agreement. If we are successfully able to gain regulatory approval in any country for a licensed product, then we are also required to use commercially reasonable efforts to commercialize such licensed product in such country. We also have sole control and responsibility over all regulatory activities with respect to the development of licensed products.

We are permitted to further sublicense certain of our rights under the Editas License Agreement to third parties, provided that any such sublicense agreement with a third party must remain in compliance with and be consistent with the terms of the Editas License Agreement and the Broad/Harvard Head Licenses and MGH Head Licenses, as applicable. We are also responsible for any breaches of a sublicense agreement by the applicable sublicensee and are responsible for all payments due under the Editas License Agreement by operation of any such sublicense. Following the signing of the Editas License Agreement, we obtained the right to further sublicense our rights the licensed patents from Broad Institute and Harvard to third parties, provided that we comply with certain sublicensing requirements under each of the Broad/Harvard Head Licenses as if we were Editas, as well as certain other customary conditions. We have not obtained any such right from MGH allowing us to further sublicense our rights under the licensed patents from MGH to third parties and will require written consent in the event we wish to further sublicense such rights to a third party.

Upon the execution of the Editas License Agreement, we paid Editas an upfront fee of \$180,000. We also issued to Editas 1,833,333 shares of our Series A-1 Preferred Stock and 1,222,222 shares of our Series A-2 Preferred Stock. In addition, if any of our commercial, regulatory, development or sales activities with respect to the licensed products triggers a milestone payment or sublicense income that Editas owes under the Broad/Harvard Head Licenses or the MGH Head Licenses, then we are required to pay Editas the full amount of such milestone payment or sublicense income, as applicable; provided that we will not pay Editas for any sublicense income due as a result of the upfront fee we paid to Editas, our issuance of Series A-1 Preferred Stock and Series A-2 Preferred Stock to Editas, or our payment of any option exercise fee to Editas. Aggregate milestone amounts under the Editas License Agreement could equal up to \$68.8 million for each product developed and commercialized using rights related to certain base editing technologies and CRISPR technology; in the event we develop and commercialize products covered by claims from the additional patent families licensed or optioned to us under the Editas License Agreement, aggregate milestone payments could equal up to \$74.0 million per product. The percentage of sublicense income we would owe under the Editas License Agreement ranges from none to amounts between 10% and 20%. In addition, we agreed to pay for a portion of the annual license maintenance fees and prosecution and maintenance costs that Editas incurs itself or owes under the Broad /Harvard Head Licenses and the MGH Head Licenses with respect to the licensed patents. The upfront fee, equity issuance, and option exercise payments we make to Editas under the Editas License Agreement constitute both consideration for the licenses granted to us under the Editas License Agreement and reimbursement for prosecution and maintenance costs for the licensed patents.

With respect to the sale of licensed products by us, our affiliates or our sublicensees, we are required to pay to Editas an amount equal to the royalty rates that it owes to Broad Institute, Harvard, or MGH under its applicable in-licenses, plus an additional low- to mid-single digit royalty on net sales of licensed products, depending on whether such licensed product is covered by an Editas-owned patent and based on the aggregate worldwide net sales of licensed products in a given calendar year. We are entitled to certain reductions and offsets on these royalties with respect to a licensed product in a given country and if Editas is entitled to receive any reductions or offsets in respect to its royalty payment obligations under the relevant Broad/Harvard Head Licenses or MGH Head Licenses, then Editas will use reasonable efforts to avail itself of such reductions, which in turn would reduce our royalty payment obligations under the Editas License Agreement. The royalty term expires on licensed product-by-licensed product and country-by-country basis upon the later of (i) the last-to-expire royalty term in such country under any applicable Broad/Harvard Head License or MGH Head License, and, if such product is covered by a licensed Editas-owned patent, (ii) the date at which such product is no longer covered by a valid claim of a licensed Editas-owned patent in such country.

As between the parties, Editas is responsible for the prosecution and maintenance of all licensed patents, provided that we have certain information, comment, and review rights for certain of the licensed patents.

Unless earlier terminated, the Editas License Agreement will expire on a licensed product-by-licensed product and country-by-country basis on the expiration of the applicable royalty term with respect to such licensed product in such country. We may terminate the Editas License Agreement on written notice to Editas subject to a specified notice period. Either party may terminate the Editas License Agreement for a material breach of the other party, subject to a notice and cure period. Editas may also terminate the Editas License Agreement if we challenge the validity of any of the licensed patents, subject to customary carveouts. Upon expiration or termination of the Editas License Agreement in its entirety or with respect to a family of patents, the licenses granted to us will immediately terminate in its entirety or solely with respect to the expired or terminated patent family, as the case may be; however, if we have the right to terminate the Editas License Agreement due to Editas' material breach of the Editas License Agreement, then in lieu of so terminating the Editas License Agreement, we can elect to reduce our royalty payment obligations under the Editas License Agreement by certain specified percentages.

#### ***License Agreement with The Broad Institute, Inc.***

In May 2018, our affiliate, Blink Therapeutics Inc., or Blink, entered into a license agreement, as amended, or the Broad License Agreement, with Broad Institute. In September 2021, Blink merged with and into Beam, such that Blink's separate corporate existence ceased and Beam continued as the surviving corporation and the successor by merger to the Broad License Agreement with respect to Blink. Under the Broad License Agreement, and as further detailed below, we received certain rights to RNA base editing technology, including the RNA editor platforms RESCUE™ and REPAIR™, which use Cas13 linked to a deaminase to deliver single base A-to-I or C-to-U editing of RNA transcripts, respectively, as well as the Cas12b nuclease family of gene editing enzymes.

More specifically, under the Broad License Agreement, Broad Institute granted us an exclusive, worldwide, royalty-bearing and sublicensable license under certain patent rights to the extent owned or controlled by Broad Institute (including via an interinstitutional agreement with the Massachusetts Institute of Technology, or MIT, and Harvard) comprising (i) certain patent rights claiming or disclosing novel CRISPR enzymes and systems (including those related to DNA cleaving) or systems, methods and compositions for targeted nucleic acid editing, in each case to exploit products covered by such patents, (ii) certain product-specific patent rights claiming or disclosing novel CRISPR enzymes and systems, methods and compositions for targeted nucleic acid editing, in each case to exploit base editor products covered by such patents and (iii) certain patent rights generally related to gene targeting to exploit base editor products covered by such patents, in each case to make, have made, offer for sale, sell, have sold and import certain licensed products.

Under the Broad License Agreement, we have also been granted (i) a non-exclusive, royalty-bearing and sublicensable license under all patents exclusively licensed to us under the Broad License Agreement to make, have made, offer for sale, sell, have sold and import certain products in our field that were made, discovered, developed or determined to have utility through the use of such patents in a research or discovery program commencing before May 2021 or through the use of transferred materials from Broad Institute but that are not covered by the licensed patents and (ii) a non-exclusive, worldwide, royalty-bearing and sublicensable internal research license under all patents exclusively licensed to us. All licenses granted to us by Broad Institute exclude human germline modification, the stimulation of biased inheritance of particular genes or, with certain exceptions, traits within a plant or animal population and certain modifications of the tobacco plant and are subject to certain retained rights of Broad Institute, Harvard and MIT and the U.S. federal government. Broad Institute additionally retains limited rights for itself, Harvard and MIT and for other non-profit research organizations to practice the licensed patents for research, educational, and scholarly purposes.

Under the Broad License Agreement, we are required to use commercially reasonable efforts to develop licensed products in accordance with a development plan that Blink prepared and submitted to Broad Institute. The development plan includes certain development milestones that we are required to meet, as well as the timelines for the completion thereof, and we may update the development plan from time to time if we believe, in our good faith judgment, that such update is needed in order to improve our ability to meet such development milestones. We will not be able to delay such development milestone timelines without providing a reasonable explanation and plan to Broad Institute and provided further that Broad Institute's approval of the explanation and plan in its reasonable discretion is required for any milestone timeline extension of more than a specified number of years. If we are successfully able to gain regulatory approval in any country to introduce a licensed product into the commercial market in such country, then we are also required to use commercially reasonable efforts to commercialize such licensed product and make such licensed product reasonably available to the public.

Additionally, we are required to use commercially reasonable efforts to pursue the viability of the technology covered, claimed or disclosed in certain sub-categories of licensed patents and must initiate a discovery program for the development of a licensed product covered by a valid claim, or otherwise generally enabled, by the use of such sub-category of the licensed patents during a certain period of time following the execution of the Broad License Agreement and submit an updated development plan and development milestones reasonably acceptable to Broad Institute for such sub-category of the licensed patents within such period of time. If we fail to use commercially reasonable efforts to pursue the viability of such technology or to initiate a discovery program or to submit an updated development plan in the specified time period then the license under such sub-category of the licensed patents will terminate and, if such sub-category of the licensed patents consists of base editor patent rights, our rights with respect to gene targeting licensed patents shall convert to non-exclusive so that such rights may be licensed for use to such terminated base editor licensed patents.

Broad Institute, MIT, and Harvard also retain the right to grant further licenses under specified circumstances to third parties, other than specified entities, that wish to research, develop, and commercialize a product that would otherwise fall within the scope of our exclusive license grant from Broad Institute and Harvard pursuant to Broad Institute, Harvard and MIT's inclusive innovation model. If, after a specified period of time, such a third party inquires with Broad Institute for such a license and presents to Broad Institute a proposal including information describing the proposed development and commercialization of such a proposed product, then Broad Institute may notify us of the request and the requester's identity, and the nature of the specific proposed product, including the applicable gene to which the proposed product is directed. Broad Institute is not required to share any other information provided by the requester to us in connection with the inclusive innovation model. If we are not researching, developing or commercializing such a proposed product, then we can notify Broad Institute as to whether in good faith we are interested in developing such proposed product, entering into a sublicense agreement with such requesting third party to develop such proposed product, entering into a sublicense with another third party to develop such proposed product, or that we are not interested in any of the foregoing. If we inform Broad Institute that we are interested in developing such proposed product, then we will prepare a development plan, similar in scope to the development plan under the Broad License Agreement, to develop such proposed product and must commence the development program for such proposed product within a specified period. If we inform Broad Institute that we are interested in entering into a sublicense agreement pursuant to which the inquiring third party or another third party would receive a sublicense from us under the licensed patents to develop such proposed product, then we may enter into such a sublicense agreement and provide reasonable evidence thereof during the period. If we decline to conduct the foregoing activities or do not complete such activities within the specified period, which period is reduced by the period of time the requesting third party has previously negotiated with us, then Broad Institute may grant a license to the applicable third party under the licensed patents to research, develop, and commercialize such proposed product, and our license to such the applicable patent rights will, at Broad Institute's election, terminate with respect to the gene that is the subject of the proposed third party product.

We are permitted to sublicense the licensed patents to affiliates and third parties, provided that any such sublicense agreement must remain in compliance with and be consistent with the terms of the Broad License Agreement. In addition, any such sublicense agreement must include certain customary provisions to ensure our ability to comply with the Broad License Agreement. We are also responsible for any breaches of a sublicense agreement by the applicable sublicensee and are responsible for all payments due under the Broad License Agreement by operation of any such sublicense.

As partial consideration for the rights granted under the Broad License Agreement, Broad Institute received 1,940,000 shares of Blink's common stock. The shares issued to Broad Institute were exchanged into 865,240 shares of our common stock in connection with our acquisition of Blink on September 25, 2018.

Under the Broad License Agreement, we are also required to pay Broad Institute an annual license maintenance fee ranging from the low- to mid-five figures to the low-six figures, depending on the particular calendar year. Broad Institute is also entitled to receive clinical and regulatory milestones totaling in the mid-to-high eight figure range. We paid Broad Institute a total of \$9.0 million upon the completion of our Series A and Series B financings.

In May 2021, the first success payment measurement occurred and amounts due to Broad Institute were calculated to be \$15.0 million. We elected to make the payment in shares of our common stock and issued 174,825 shares of our common stock to settle this liability on June 10, 2021. We may additionally owe Broad Institute success payments of up to an additional \$90.0 million.

We are also required to pay royalties in the low single digits for products covered by the licensed patents with such royalty reduced by a certain percentage for products enabled by the licensed patents or transferred materials, but not covered by the licensed patents. The royalty rate payable by us is subject to customary reductions and offsets on these royalties with respect to a product in a given country. The royalty term for a product in a country will terminate on the later of the expiration of (i) the last to expire licensed patent covering the applicable product, (ii) the period of exclusivity associated with such product in such country or (iii) a certain period of time after the first commercial sale of such product in such country. If we sublicense our rights to develop or commercialize a licensed product under the Broad License Agreement to a third party and receive non-royalty sublicense income, then Broad Institute is entitled to a percentage of such consideration, ranging from the high single digits to an amount in the low first decile, dependent on the development stage of products under the Broad License Agreement at the time of sublicense execution.

Broad Institute is responsible for the prosecution and maintenance of all licensed patents, provided that we have certain consultation, comment, and review rights with respect to such prosecution and maintenance activities of exclusively licensed patent rights.

Unless earlier terminated, the Broad License Agreement will remain in effect until the later of the last-to-expire valid claim of a licensed patent covering our licensed products or the end of the last to expire royalty term. We may terminate the Broad License Agreement for its convenience following written notice to Broad Institute subject to a specified notice period. Either party may terminate the Broad License Agreement for a material breach of the other party, subject to a notice and cure period. Broad Institute may also terminate the Broad License Agreement in the event of our bankruptcy or insolvency, if we fail to procure and maintain insurance or if we, our affiliates or sublicensees bringing patent challenges relating to any licensed patents (subject to a cure period for us to terminate the sublicensee that has taken the applicable action).

### ***License Agreement with Bio Palette Co., Ltd.***

On March 27, 2019, we entered into a license agreement, or the Bio Palette License Agreement, with Bio Palette Co., Ltd., or Bio Palette, pursuant to which we received an exclusive (even as to Bio Palette and its affiliates), sublicensable license under certain patent rights related to base editing owned or controlled by Bio Palette to research, make, have made, import, export, distribute, use, have used, sell, have sold or offer for sale, and otherwise exploit products for the treatment of human disease throughout the world, but excluding products in the microbiome field in Asia. In addition, we granted Bio Palette an exclusive (even as to us and our affiliates) license under certain patent rights related to base editing and gene editing owned or controlled by us to research, make, have made, import, export, distribute, use, have used, sell, have sold or offer for sale, and otherwise exploit products in the microbiome field in Asia, subject to our right, in its sole discretion, to expand Bio Palette's license (and the applicable royalty obligations) to the entire territory. Each party to the Bio Palette Agreement retains non-exclusive rights to develop and manufacture products in the microbiome field worldwide for the sole purpose of exploiting those products in its own territory. Each party agrees to certain coordination obligations in the microbiome field in the event that either party determines not to exploit their rights in such field.

If Bio Palette comes into the control of any other patent right that is useful for the treatment, diagnosis or prevention of any human diseases or conditions and intends to grant a license under that patent right in certain defined fields and in certain defined territories, we have the exclusive right of first negotiation for an exclusive license under that patent right in those fields and territories. If we come into the control of any other patent right that is useful in certain defined fields and intend to grant a license under that patent right in those fields in certain defined territories, Bio Palette has the exclusive right of first negotiation for an exclusive license under that patent right in those fields and territories.

As part of the Bio Palette License Agreement, if we form a Scientific Advisory Board, then Bio Palette will have the right to appoint two representatives to such board until the conclusion of the period ending five years after the effective date of the Bio Palette License Agreement. Additionally, we and Bio Palette agree to communicate with each other regarding potential base editing collaborations in Japan.

We are required to use commercially reasonable efforts to develop a licensed product in the United States, Japan, the U.K., France, Germany, Italy and Spain. For any licensed product in our licensed field and territory that receives regulatory approval, we are required to use commercially reasonable efforts to commercialize that licensed product in the relevant country. Bio Palette is required to use commercially reasonable efforts to develop a licensed product in Japan. For any licensed product that receives regulatory approval, Bio Palette is required to use commercially reasonable efforts to commercialize such licensed product in the relevant country.

Certain of the patents licensed to us under the Bio Palette License Agreement were licensed to Bio Palette from Kobe University under a license agreement we refer to as the Kobe Head License. Accordingly, the licenses granted to us under the Bio Palette License Agreement are subject to the terms and conditions set forth in the Kobe Head License, which include provisions providing for certain rights to be retained by third parties including governmental authorities.

We and Bio Palette are both permitted to sublicense the licensed patents to affiliates and third parties, provided that the applicable terms of the Bio Palette License Agreement and the Kobe Head License would apply to such affiliates and third parties. The sublicensing party is also responsible for any breaches of such terms by the applicable sublicensee and is responsible for all payments due under the Bio Palette License Agreement by operation of any such sublicense.

Upon the execution of the Bio Palette License Agreement, we paid Bio Palette an upfront fee of \$0.5 million. In connection with the execution of the Bio Palette License Agreement, we issued to Bio Palette 16,725 shares of our common stock, with an agreement to issue additional shares of our common stock in the low six figures in the event that the referenced Bio Palette patent issues in the United States. Upon the issuance of a certain Bio Palette patent in the United States in June 2020, we made a milestone payment to Bio Palette of \$2.0 million and, in July 2020, issued to Bio Palette 175,000 shares of our common stock valued at \$0.3 million. We also agreed to pay a royalty at a fraction of a percent on net sales of products that are covered by the patents licensed by Bio Palette to us, and Bio Palette agreed to pay a royalty at a fraction of a percent on net sales of products that are covered by the patents licensed by us to Bio Palette. The royalty term for a product in a country will terminate on the later of the expiration of (i) patent-based exclusivity with respect to such licensed product in such country or (ii) regulatory exclusivity with respect to such licensed product in such country.

Any intellectual property arising out of activities under the Bio Palette License Agreement will be owned by the party inventing such intellectual property. Bio Palette is responsible for the prosecution and maintenance of all patents licensed by Bio Palette to us, provided that we have customary consultation, comment and review rights with respect to such prosecution and maintenance activities solely with respect to national entries of a certain specified PCT application. We have the sole right to prosecute and maintain patents licensed by us to Bio Palette.

Unless earlier terminated, the Bio Palette License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of the applicable royalty term for each such licensed product and country. Each party has the right to terminate the Bio Palette License Agreement for convenience with respect to the license granted to such party subject to a specified notice period. Either party may terminate the Bio Palette License Agreement with respect to the license granted to the other party for a material breach by the other party, subject to a specified notice and cure period. Additionally, either party may also terminate the Bio Palette License Agreement in the event of the other party's bankruptcy or insolvency or if the other party, its affiliates or sublicensees brings a patent challenge relating to any licensed patents (but, in the case of such a patent challenge by a sublicensee, subject to a cure period for such party to terminate its agreement with the sublicensee that has taken the applicable action).

### **Government regulation**

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the EU, extensively regulate, among other things, the research, development, testing, manufacturing, packaging, labeling, storage, record keeping, reimbursement, advertising, promotion, distribution, post-approval monitoring and reporting and import and export, pricing and reimbursement of pharmaceutical products, including biological products. Failure to comply with the applicable regulatory requirements at any time during the product development process or post-approval may subject an applicant for marketing approval to delays in development or approval, as well as administrative and judicial sanctions.

The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions and compliance with applicable statutes and regulatory requirements, both pre- and post-approval, and obtaining reimbursement status will continue to require the expenditure of substantial time and financial resources. The regulatory requirements applicable to drug and biological product development, approval, and marketing are subject to change, and regulations and administrative guidance often are revised or reinterpreted by the agencies in ways that may have a significant impact on our business. Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use.

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

In the United States, our candidate products are regulated as biological products, or biologics, under the Public Health Service Act, or the PHSA, and the Federal Food, Drug and Cosmetic Act, or the FDCA, the implementing regulations of the FDA and other federal, state and local statutes and regulations.

The FDA must approve a product candidate for a therapeutic indication before it may be marketed in the United States. 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 Practice, 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;
- design of a clinical protocol and 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 Biologics License Application, or BLA, requesting marketing of the biological product for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product and proposed labelling;
- review of the BLA by an FDA advisory committee, where 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 current Good Manufacturing Practices, or cGMP, requirements; to assure that the facilities, methods, and controls are adequate to preserve the product's identity, strength, quality, and purity; and, if applicable, the FDA's current good tissue practice, or cGTP, requirements for the use of human cellular and tissue products;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GLPs and GCPs and the integrity of clinical data in support of the BLA;

- payment of the application fee under the Prescription Drug User Free Act, or PDUFA, unless exempted; and
- FDA review and approval of the BLA, which may be subject to additional post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and any post-approval studies required by the FDA.

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

Before testing any investigational biological product in humans, including a gene editing 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, including GLP regulations and standards and the United States Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application.

An IND is an exemption from the FDCA that allows an unapproved drug or biological product to be shipped in interstate commerce for use in an investigational clinical trial. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved new drug application, or NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An 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. Preclinical or nonclinical testing typically continues even after the IND is submitted.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a partial clinical hold might state that a specific protocol or part of a protocol may not proceed, while other parts of a protocol or other protocols may do so. No more than 30 days after the imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following the issuance of a clinical hold or partial clinical hold, a clinical investigation may only resume once the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed or recommence. Occasionally, clinical holds are imposed due to manufacturing issues that may present safety issues for the clinical study subjects.

Additionally, genetic medicine 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 U.S. National Institutes of Health's, or 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 genetic medicine 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. 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.

There is no requirement for a manufacturer to provide expanded access to an investigational product. However, if a manufacturer decides to make its investigational product available for expanded access, FDA reviews requests for expanded access and determines if treatment may proceed. Expanded access may be appropriate 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.



Under the FDCA, sponsors of one or more investigational products for the treatment of a serious disease(s) or condition(s) must make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the investigational drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides an additional mechanism for patients with a life-threatening condition who have exhausted approved treatments and are unable to participate in clinical trials to access certain investigational products that have completed a Phase I clinical trial, are the subject of an active IND, and are undergoing investigation for FDA approval. Unlike the expanded access framework described above, the Right to Try Pathway does not require FDA to review or approve requests for use of the investigational product. There is no obligation for a manufacturer to make its investigational products available to eligible patients under 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 to be treated under the supervision of qualified principal investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent for their participation. Clinical trials are conducted under study protocols detailing, among other things, the objectives of the study, 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 FDA regulatory requirements in order to use the trial as support for an IND or application for marketing approval in the U.S. Specifically, the FDA requires that such trials be conducted in accordance with GCP requirements intended to ensure the protection of human subjects and the quality and integrity of the study data, including requirements for review and approval by an independent ethics committee and obtaining subjects' informed consent.

For clinical trials conducted in the United States, an IND is required, and 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. Clinical trials must also comply with extensive GCP rules and the requirements for obtaining subjects' informed consent. 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, including GCP, or the subjects or patients are being exposed to an unacceptable health risk.

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 committee. This group may recommend continuation of the study as planned, changes in study conduct, or cessation of the study at designated checkpoints based on access to certain data from the study. Finally, research activities involving infectious agents, hazardous chemicals, recombinant DNA, and genetically altered organisms and agents may be subject to review and approval of an Institutional Biosafety Committee, or IBC, in accordance with NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules.

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 the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, 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. Clinical trials are undertaken within an expanded patient population at multiple geographically dispersed clinical study sites to further evaluate dosage, provide substantial evidence of clinical efficacy, and further test for safety. 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.”
- A clinical trial may combine the elements of more than one phase and the FDA often requires more than one *Phase 3* trial to support marketing approval of a product candidate. A company’s designation of a clinical trial as being of a particular phase is not necessarily indicative that the study will be sufficient to satisfy the FDA requirements of that phase because this determination cannot be made until the protocol and data have been submitted to and reviewed by the FDA. Moreover, as noted above, a pivotal trial is a clinical trial that is believed to satisfy FDA requirements for the evaluation of a product candidate’s safety and efficacy such that it can be used, alone or with other pivotal or non-pivotal trials, to support regulatory approval. Generally, pivotal trials are *Phase 3* trials, but they may be *Phase 2* trials if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

In some cases, the FDA may approve a BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate’s safety or 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. Failure to exhibit due diligence with regard to conducting *Phase 4* clinical trials could result in withdrawal of approval for products. The FDA generally recommends that sponsors observe subjects for potential gene-therapy related delayed adverse events in a long-term follow-up study of fifteen years for integrating vectors, up to fifteen years for herpes virus vectors capable of establishing latency, up to fifteen years for microbial vectors known to establish persistent infection, up to fifteen years for gene editing products, and up to five years for AAV vectors. FDA recommends that these long-term follow-up studies include, at a minimum, five years of annual physical examinations followed by annual queries, either in-person or by phone or written questionnaire, for the remaining observation period.

Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the occurrence of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. *Phase 1*, *Phase 2* and *Phase 3* clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

In response to the COVID-19 pandemic, the FDA issued guidance on March 18, 2020, and has updated it periodically since that time to address the conduct of clinical trials during the pandemic. The guidance sets out a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical study report (or as a separate document) contingency measures implemented to manage the study, and any disruption of the study as a result of COVID-19; a list of all study participants affected by COVID-19-related study disruptions by a unique subject identifier and by investigational site, and a description of how the individual’s participation was altered; and analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study, among other things. The FDA has indicated that it will continue to provide any necessary guidance to sponsors, clinical investigators, and research institutions as the public health emergency evolves.

During the development of a new product candidate, sponsors are given opportunities to meet with the FDA at certain points; specifically, prior to the submission of an IND, at the end of *Phase 2* and before an application is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date and for the FDA to provide advice on the next phase of development. Sponsors typically use the meeting at the end of *Phase 2* to discuss their *Phase 2* clinical results and present their plans for the pivotal *Phase 3* clinical trial that they believe will support the approval of the new product.

Sponsors of clinical trials of certain FDA-regulated products, including prescription drugs, are required to register and disclose certain clinical trial information on a public registry maintained by the NIH. In particular, information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Although sponsors are also obligated to disclose the results of their clinical trials after completion, disclosure of the results can be delayed in some cases for up to two years after the date of completion of the trial. Failure to timely register a covered clinical study or to submit study results as provided for in the law can give rise to civil monetary penalties and also prevent the non-compliant party from receiving future grant funds from the federal government. The NIH’s Final Rule on ClinicalTrials.gov registration and reporting requirements became effective in 2017, and both the NIH and the FDA have recently signaled the government’s willingness to begin enforcing those requirements against non-compliant clinical trial sponsors.

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 submit a pediatric study plan, or PSP, within 60 days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. The PSP outlines the proposed pediatric study or studies they plan to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The FDA must then review the information submitted, consult with the sponsor, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For investigational 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, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than 90 days after FDA's receipt of the study plan. The FDA may, on its own initiative or at the request of the 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, under specified circumstances. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease. The FDA also maintains a list of diseases that are exempt from PREA requirements due to low prevalence of disease in the pediatric population.

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

It is possible that the procedures and standards applied to gene therapy products and cell therapy products may be applied to any CRISPR/Cas9 product candidates we may develop, but that remains uncertain at this point. The FDA has defined a gene therapy product as one that mediates its effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and which are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells *in vivo* or be transferred to cells *ex vivo* prior to administration to the recipient. The Center for Biologics Evaluation and Research, or CBER, at FDA regulates gene therapy products. Within CBER, the review of gene therapy and related products is consolidated in the Office of Tissues and Advanced Therapies, and the FDA has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its reviews. CBER works closely with the NIH, and the FDA and the NIH have published a number of guidance documents with respect to the development of gene therapy products.

Although the FDA's guidance documents are not legally binding, we believe that our compliance with certain aspects of them is likely necessary to gain approval for any product candidate we may develop. The guidance documents provide recommendations and additional clarity as to factors that the FDA will consider at each stage of gene therapy development and relate to, among other things, the proper preclinical assessment of gene therapies; the chemistry, manufacturing, and controls, or CMC, information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies; and gene therapy products for the treatment of rare diseases. Further, the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire.

If a gene therapy trial is conducted at, or sponsored by, institutions receiving any NIH funding for research involving recombinant or synthetic nucleic acid molecules, the trial must be conducted in accordance with the NIH Guidelines for Research Involving Recombinant DNA Molecules. Research conducted at such institutions that involves the transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human subjects must undergo review and approval by an IBC before it commences. Many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

### *Compliance with cGMP and cGTP requirements*

The FDA's regulations require that pharmaceutical products be manufactured in specific approved facilities and in accordance with cGMPs. The cGMP regulations include requirements relating to organization of personnel, buildings and facilities, equipment, control of components and drug product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports and returned or salvaged products. Manufacturers and other entities involved in the manufacture and distribution of approved pharmaceuticals are required to register their establishments with the FDA and some state agencies and are subject to periodic unannounced inspections by the FDA for compliance with cGMPs and other requirements. 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. Changes to the manufacturing process, specifications or container closure system for an approved product are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require, among other things, the investigation and correction of any deviations from cGMP and the imposition of reporting and documentation requirements upon the NDA sponsor and any third-party manufacturers involved in producing the approved product.

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. Material changes in manufacturing equipment, location, or process post-approval, may result in additional regulatory review and approval.

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

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. The manufacturing facilities may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. If a manufacturing facility is not in substantial compliance with the applicable regulations and requirements imposed when the product was approved, regulatory enforcement action may be taken, which may include a warning letter or an injunction against shipment of products from the facility and/or recall of products previously shipped.

### *Review and approval of a BLA*

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, along with information relating to the product's chemistry, manufacturing, controls and proposed labeling, are submitted to the FDA as part of an application requesting approval to market the product candidate for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety, potency and purity of the investigational product to the satisfaction of the FDA. The fee required for the submission of a BLA under the Prescription Drug User Fee Act, or PDUFA, is substantial (for example, for FY2022 this application fee is approximately \$3.1 million), and the sponsor of an approved NDA is also subject to an annual program fee, currently more than \$369,000 per eligible prescription drug product. These fees are typically adjusted annually, and exemptions and waivers may be available under certain circumstances, such as where a waiver is necessary to protect the public health, where the fee would present a significant barrier to innovation, or where the applicant is a small business submitting its first human therapeutic application for review.

The FDA conducts a preliminary review of the BLA within 60 days of receipt and must inform the sponsor by that time whether the application is sufficiently complete to permit substantive review. In pertinent part, the FDA's regulations for applications state that an application "shall not be considered as filed until all pertinent information and data have been received" by the FDA. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refuse to File, or RTF, determination to the applicant. Typically, an RTF will be based on administrative incompleteness, such as clear omission of information or sections of required information; scientific incompleteness, such as omission of critical data, information or analyses needed to evaluate safety, purity and potency or provide adequate directions for use; or inadequate content, presentation, or organization of information such that substantive and meaningful review is precluded. The FDA may request additional information rather than accept a BLA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing.

After the submission is accepted for filing, the FDA begins an in-depth substantive review of the application. The FDA may inform the applicant of certain requirements for information when it accepts the BLA or by the 74<sup>th</sup> day of the receipt of the BLA. Thereafter, the FDA may submit “information requests” to the applicant in the course of the agency’s review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and effective for its intended use, whether it has an acceptable purity profile and whether the product is being manufactured in accordance with cGMP. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard application for an investigational product that is a new molecular entity, and six months from the filing date for an application with “priority review.” The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission. Despite these review goals, it is not uncommon for FDA review of a BLA to extend beyond the PDUFA goal date.

Before approving a BLA, the FDA may inspect the sponsor and one or more clinical trial sites to assure compliance with IND and GCP requirements and the integrity of the clinical data submitted to the FDA. Additionally, the FDA may refer the BLA, including applications for novel product candidates which present difficult questions of safety or efficacy, to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. 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 recommendation of an advisory committee, but it considers such recommendations when making final decisions on approval. Data from clinical trials are not always conclusive, and the FDA or its advisory committee may interpret data differently than the NDA sponsor interprets the same data. The FDA may also re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process.

The FDA reviews a BLA to determine, among other things, whether the product is safe and whether it is effective for its intended use(s), with the latter determination being made on the basis of substantial evidence. The term “substantial evidence” is defined under the FDCA as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

The FDA has interpreted this evidentiary standard to require at least two adequate and well-controlled clinical investigations to establish effectiveness of a product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional information may satisfy this standard. This approach was subsequently endorsed by Congress in 1998 with legislation providing, in pertinent part, that “If [the FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, FDA may consider such data and evidence to constitute substantial evidence.” This modification to the law recognized the potential for the FDA to find that one adequate and well controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness. In December 2019, the FDA issued draft guidance further explaining the studies that are needed to establish substantial evidence of effectiveness. It has not yet finalized that guidance.

In addition, before approving an application, the FDA will determine whether the facility in which the product is manufactured, processed, packed or held meets standards designed to assure the product’s continued safety. The approval process is lengthy and often difficult, and the FDA may refuse to approve a BLA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data and information. After evaluating the application and all related information, including the advisory committee recommendations, if any, and inspection reports of manufacturing facilities and clinical trial sites, the FDA may issue either an approval letter or a Complete Response Letter, or CRL.

An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the applicant may either resubmit the NDA addressing all of the deficiencies identified in the letter or withdraw the application. If and when those deficiencies have been addressed to the FDA’s satisfaction in a resubmission of the BLA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with the submission of this additional information, however, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a new product, it may limit the approved indications 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 require post-approval studies, including Phase 4 clinical trials, to further assess the product's safety or efficacy 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.

#### *Fast track, breakthrough therapy, priority review and regenerative advanced therapy designations*

The FDA has several programs designed to expedite the development and approval of drugs and biological products intended to treat serious or life-threatening diseases or conditions. These programs include fast track designation, breakthrough therapy designation, priority review designation, and regenerative medicine advanced therapy (RMAT) designation. These designations are not mutually exclusive, and a product candidate may qualify for one or more of these programs. While these programs are intended to expedite product development and approval, they do not alter the standards for FDA approval.

The FDA may grant a product fast track designation if it is intended for the treatment of a serious or life-threatening disease or condition, and nonclinical or clinical data demonstrate the potential to address an unmet medical need for such disease or condition. 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 marketing application before the application is complete in some circumstances. Fast track designation may be rescinded if FDA believes that the product no longer meets the qualifying criteria.

A product may be designated as a breakthrough therapy if it is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to aid sponsors in designing the clinical trials in an efficient manner. Breakthrough designation may be rescinded if a product no longer meets the qualifying criteria.

With passage of the 21st Century Cures Act in December 2016, Congress authorized an additional expedited program for regenerative medicine advanced therapies. A product is eligible for RMAT designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of RMAT designation include the benefits available to breakthrough therapies, including potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints. RMAT designation may be rescinded if a product no longer meets the qualifying criteria.

FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of such condition. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and it shortens the FDA's goal for taking action on a marketing application from ten months to six months.

#### *Accelerated approval pathway*

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.

The accelerated approval pathway is most often used in settings in which the course of a disease is long, and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

For drugs granted accelerated approval, FDA generally requires sponsors to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. Failure to conduct required post-approval studies with due diligence, failure to confirm a clinical benefit during the post-approval studies, or dissemination of false or misleading promotional materials would allow the FDA to withdraw the product approval on an expedited basis. All promotional materials for product candidates approved under accelerated approval are subject to prior review by the FDA unless FDA informs the applicant otherwise.

#### *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 has imposed as part of the approval process. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

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

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about a product;
- mandated modification of promotional materials and labeling and issuance of corrective information;
- 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;
- injunctions or the imposition of civil or criminal penalties; and
- consent decrees, corporate integrity agreements, debarment, or exclusion from federal health care programs.

The FDA strictly regulates the advertising and labeling of prescription drug products, including biological products. 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. In addition, the sponsor of an approved drug in the United States may not promote that drug for unapproved, or off-label, uses, although a physician may prescribe a drug for an off-label use in accordance with the practice of medicine. If a company is found to have promoted off-label uses, it may become subject to administrative and judicial enforcement by the FDA, the DOJ, 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.

After approval, some types of changes to the approved product, such as adding new indications or dosing regimens, manufacturing changes, or additional labeling claims, are subject to further FDA review and approval. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved products that have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs.

The FDA may withdraw product approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency or issues with manufacturing processes, 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 signals; 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;
- 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.

Finally, if there are any modifications to the product, including changes in indications, labeling or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new BLA or a BLA supplement, which may require the applicant to develop additional data or conduct additional preclinical studies and clinical trials. Securing FDA approval for new indications is similar to the process for approval of the original indication and requires, among other things, submitting data from adequate and well-controlled clinical trials to demonstrate the product's safety and efficacy in the new indication. Even if such trials are conducted, the FDA may not approve any expansion of the labeled indications for use in a timely fashion, or at all. There also are continuing, annual user fee requirements that are now assessed as program fees for certain approved drugs.

#### *Orphan drug designation and exclusivity*

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for the 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 the product available for the disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation qualifies a company for certain tax credits. In addition, if a drug candidate that has orphan drug designation subsequently receives the first FDA approval for that drug for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years following product approval unless the subsequent product candidate is demonstrated to be clinically superior. Absent a showing of clinical superiority, FDA cannot approve the same product made by another manufacturer for the same indication during the market exclusivity period unless it has the consent of the sponsor or the sponsor is unable to provide sufficient quantities.

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. To qualify for orphan exclusivity, however, the drug must be clinically superior to the previously approved product that is the same drug for the same condition.

Gene therapy products present novel issues for assessing when two products are the "same" for orphan exclusivity purposes. In September 2021, the FDA issued a final guidance document describing its current thinking on when a gene therapy product is the "same" as another product for the purpose of orphan exclusivity. Under the guidance, if either the transgene or vector differs between two gene therapy products in a manner that does not reflect "minor" differences, the two products would be considered different drugs for orphan drug exclusivity purposes. FDA will determine whether two vectors from the same viral class are the same on a case-by-case basis and may consider additional key features in assessing sameness. While the guidance provides some additional clarity on FDA's approach to assessing "sameness," significant ambiguity and uncertainty remain as to how FDA will assess viral vectors in the same class, what differences in vector or transgene are considered minor, and what additional features may be considered.



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 in December 2020, the requirement for a product to show clinical superiority applies to drugs and biologics that received orphan drug designation before enactment of the FDA Reauthorization Act of 2017, or FDARA, in 2017, but have not yet been approved or licensed by the FDA.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of exclusivity, the term “same disease or condition” in the statute means the designated “rare disease or condition” and could not be interpreted by the agency to mean the “indication or use.” Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the “indication or use.” It is unclear how this court decision will be implemented by the FDA.

#### *Pediatric exclusivity*

Pediatric exclusivity is another type of non-patent regulatory exclusivity in the United States. Specifically, the Best Pharmaceuticals for Children Act provides for the attachment of an additional six months of exclusivity, which is added on to the term of any remaining regulatory exclusivity at the time the pediatric exclusivity is granted. 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, even if the data do not show the product to be effective in the pediatric population studied.

#### *Biosimilars and exclusivity*

The 2010 Patient Protection and Affordable Care Act, or PPACA, 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.

Under the BPCIA, a manufacturer may submit an application for licensure of a biological product that is “biosimilar to” or “interchangeable with” a previously approved biological product or “reference product.” In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and 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 first licensed. This 12-year exclusivity period is referred to as the reference product exclusivity period and bars approval of a biosimilar but notably does not prevent approval of a competing product pursuant to a full BLA (i.e., containing the sponsor’s own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity, and potency of the product). The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. The law also includes an extensive process for the innovator biologic and biosimilar manufacturer to litigate patent infringement, validity, and enforceability prior to the approval of the biosimilar.

Since the passage of the BPCIA, many states have passed laws or amendments to laws, including laws governing pharmacy practices, which are state-regulated, to regulate the use of biosimilars.

#### *Patent term restoration and extension*

A patent claiming a new biological product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for a single patent for an approved product as compensation for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date a clinical investigation involving human beings is begun and the submission date of a marketing application less any time during which the applicant failed to exercise due diligence, plus the time between the submission date of an application and the ultimate approval date less any time during which the applicant failed to exercise due diligence. 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. Only one patent applicable to an approved product is eligible for the extension, only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended and the application for the extension must be submitted prior to the expiration of the patent in question. 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 or restoration 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.

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

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

The FDA previously has required *in vitro* companion diagnostics intended to select the patients who will respond to the product candidate to obtain 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, which exceeds \$250,000 for most PMAs; for federal fiscal year 2022, the standard fee for review of a PMA is \$374,858 and the small business fee is \$93,714.

A clinical trial is typically required for a PMA application and, in a small percentage of cases, the FDA may require a clinical study in support of a 510(k) submission. A manufacturer that wishes to conduct a clinical study involving the device is subject to the FDA's IDE regulation. The IDE regulation distinguishes between significant and non-significant risk device studies and the procedures for obtaining approval to begin the study differ accordingly. Also, some types of studies are exempt from the IDE regulations. A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices are devices that are substantially important in diagnosing, curing, mitigating, or treating disease or in preventing impairment to human health. Studies of devices that pose a significant risk require both FDA and an IRB approval prior to initiation of a clinical study. Many companion diagnostics are considered significant risk devices due to their role in diagnosing a disease or condition. Non-significant risk devices are devices that do not pose a significant risk to the human subjects. A non-significant risk device study requires only IRB approval prior to initiation of a clinical study.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the Quality System Regulation, which covers the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

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

There are multiple privacy and data security laws that may impact our business activities in the United States and in other countries where we conduct trials or where we may do business in the future. These laws are evolving and may increase both our obligations and our regulatory risks in the future. In the health care industry generally, 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, 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. HIPAA may apply to us in certain circumstances and may also apply to our business partners in ways that may impact our relationships with them. Any clinical trials we conduct will be regulated by Subpart A of 45 CFR 46, also known as the Common Rule, which also includes specific privacy-related provisions. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that may be 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. In addition, 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. State attorneys general also have authority to enforce state privacy and security laws. Moreover, new laws and regulations governing privacy and security may be adopted in the future as well.

At the state level, in 2018, California passed into law the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. It also provides California residents a private right of action, including the ability to seek statutory damages, in the event of a breach involving their personal information. Compliance with the CCPA is 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. On November 3, 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or the CPRA, which will expand the CCPA to incorporate additional provisions, including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA will also expand personal information rights of California residents, including creating a right to opt out of sharing of personal information with third parties for advertising, expanding the lookback period for the right to know about personal information held by businesses, and expanding the right to erasure for information held by third parties. Most CPRA provisions will take effect on January 1, 2023, though the obligations will apply to any personal information collected after January 1, 2022. These provisions may apply to some of our business activities. In addition, other states, including Virginia and Colorado, already have passed state privacy laws. Other states will be considering these laws in the future. These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of any products for which we or our collaborators obtain regulatory and marketing approval.

### ***Regulation and procedures governing approval of medicinal products in the EU and the U.K.***

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 EU 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 EU.

### *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 EU has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of an EU 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 EU adopted a new Clinical Trials Regulation (EU) No 536/2014, but it has not yet become effective. The Clinical Trials Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the “EU portal”; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned). Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

The conduct of all clinical trials performed in the EU 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 January 2022.

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

#### *Marketing authorization*

To obtain a marketing authorization for a gene therapy product under the EU regulatory system, an applicant must submit an application via the centralized procedure administered by the European Medicines Agency (EMA). Specifically, the grant of marketing authorization in the EU for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation 1394/2007/EC on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation 1394/2007/EC lays down specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety, and efficacy of their products to the EMA’s Committee for Advance Therapies which provides a draft opinion regarding the application for marketing authorization and which is subject to final approval by the EMA’s Committee for Medicinal Products for Human Use. The European Commission grants or refuses marketing authorization in light of that final approval.

Under the centralized procedure in the EU, 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 Committee for Medicinal Products for Human Use, or 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.

### *Conditional approval*

In specific circumstances, E.U. legislation (Article 14—a Regulation (EC) No 726/2004 (as amended by Regulation (EU) 2019/5 and Regulation (EC) No 507/2006 on Conditional Marketing Authorizations for Medicinal Products for Human Use) enables applicants to obtain a conditional marketing authorization prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for product candidates (including medicines designated as orphan medicinal products) if (1) the product candidate is intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases; (2) the product candidate is intended to meet unmet medical needs of patients; (3) a marketing authorization may be granted prior to submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required; (4) the risk-benefit balance of the product candidate is positive; and (5) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

### *Regulatory data exclusivity in the EU*

In the EU, 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 EU from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. This also applies to biosimilars. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. In addition, if a pediatric investigation plan is accepted, then a further year of market exclusivity might be obtained (or in the alternative a patent extension (SPC) of a further 6 months). For orphan medicinal products, the periods are separate and different in that there is a total of 10-year data exclusivity and if they have a PIP, there is a further two-year extension to that 10-year period. Even if a compound is considered to be a new chemical or biological 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.

### *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 EU 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 EU'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, must also be conducted in strict compliance with the EMA's GMP requirements and comparable requirements of other regulatory bodies in the EU, which mandate the methods, facilities, and controls used in manufacturing, processing and packing of drugs to assure their safety and identity. 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 EU under Directive 2001/83/EC, as amended.

### *PRIME designation in the EU*

The EU has a Priority Medicines, or PRIME, scheme that 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.

### *Pediatric studies*

Prior to obtaining a marketing authorization in the EU, 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.

### *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 EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU 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 EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

### *Pediatric Exclusivity*

If an applicant obtains a marketing authorization in all EU 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 Supplementary Protection Certificate, or SPC.

### *Patent term extensions in the EU and other jurisdictions*

The EU also provides for patent term extension through SPCs. The rules and requirements for obtaining an 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 EU, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the EU.

## *General data protection regulation*

Similar to the laws in the United States, there are significant privacy and data security laws that apply in Europe and other countries. The collection, use, disclosure, transfer, or other processing of personal data, including personal health data, regarding individuals who are located in the European Economic Area, or the EEA, and the processing of personal data that takes place in the EEA, is subject to the EU's General Data Protection Regulation, or 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, and it imposes heightened requirements on companies that process health and other sensitive data, such as requiring in many situations that a company obtain the consent of the individuals to whom the sensitive personal data relate before processing such data. Examples of obligations imposed by the GDPR on companies processing personal data that fall within the scope of the GDPR include providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, appointing a data protection officer, 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 EEA, including the U.S., 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 is 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.

There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield framework, or Privacy Shield, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the U.S. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the U.S. While we were not self-certified under the Privacy Shield, this CJEU decision may lead to increased scrutiny on data transfers from the EU to the U.S. generally and increase our costs of compliance with data privacy legislation as well as our costs of negotiating appropriate privacy and security agreements with our vendors and business partners.

On June 23, 2016, the electorate in the U.K. voted in favor of leaving the EU, commonly referred to as Brexit. As with other issues related to Brexit, there are open questions about how personal data will be protected in the U.K. and whether personal information can transfer from the EU to the U.K. Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR. While the Data Protection Act of 2018 in the U.K. that "implements" and complements the GDPR has achieved Royal Assent on May 23, 2018 and is now effective in the U.K., it is unclear whether transfer of data from the EEA to the U.K. will remain lawful under the GDPR. The U.K. 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 U.K. to the EU/EEA remain unaffected. In addition, a recent decision from the European Commission appears to deem the U.K. as being "essentially adequate" for purposes of data transfer from the EU to the U.K., although this decision may be re-evaluated in the future.

Beyond the GDPR, there are privacy and data security laws in a growing number of countries around the world. While many loosely follow the GDPR as a model, other laws contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual sale and distribution of commercial products.

### *Brexit and the regulatory framework in the U.K.*

Following protracted negotiations, the U.K. left the EU 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 EU 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 EU directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the U.K., as the U.K. legislation now has the potential to diverge from EU legislation. It remains to be seen how Brexit will impact regulatory requirements for product candidates and products in the U.K. in the long term. The Medicines and Healthcare Regulatory Agency published detailed guidance for industry and organizations to follow from January 1, 2021 at the completion of the transition period, which the Agency will update as the U.K.'s regulatory position on medicinal products evolves over time.

### *Coverage, pricing, and reimbursement*

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any product candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of such product candidates. Sales of our products will depend, in significant part, on the availability of coverage and the adequacy of reimbursement from third-party payors.

Within the United States, third-party payors include government authorities or government healthcare programs, such as Medicare and Medicaid, and private entities, such as managed care organizations, private health insurers and other organizations. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the drug product. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Some third-party payors may manage utilization of a particular product by requiring pre-approval (known as “prior authorization”) for coverage of particular prescriptions (to allow the payor to assess medical necessity). Moreover, a third-party payor’s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain net price levels sufficient to realize an appropriate return on our investment in product development. Additionally, coverage and reimbursement for drug products can differ significantly from payor to payor. One third-party payor’s decision to cover a particular drug product or service does not ensure that other payors will also provide coverage for the drug product or will provide coverage at an adequate reimbursement rate.

Third-party payors are increasingly challenging the price and examining the cost-effectiveness of new products and services in addition to their safety and efficacy. To obtain or maintain coverage and reimbursement for any current or future product, we may need to conduct expensive pharmacoeconomic studies to demonstrate the medical necessity and cost-effectiveness of our product. These studies will be in addition to the studies required to obtain regulatory approvals. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. Thus, obtaining and maintaining reimbursement status is time-consuming and costly.

As noted above, the marketability of any product candidates for which we receive regulatory approval for commercial sale may suffer if the government and other third-party payors fail to provide coverage and adequate reimbursement. There is an emphasis on cost containment measures in the United States and we expect the pressure on pharmaceutical pricing will increase. 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 product candidates for which we receive regulatory approval from one or more third party payors, less favorable coverage policies and reimbursement rates may be implemented in the future.

If we obtain appropriate approval in the future to market any of our current product candidates in the United States, 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 EU, pricing and reimbursement schemes vary widely from country to country because this is not yet the subject of harmonized EU law. Many 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 and others with “peg” their pricing to a basket of other countries. EU 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. Some member states, in addition to controlling pricing will monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU 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 EU. The downward pressure on health care 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 EU member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.



## ***Healthcare law and regulation***

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

- federal false claims, false statements and civil monetary penalties laws prohibiting, among other things, any person from knowingly presenting, or causing to be presented, a false claim for payment of government funds or knowingly making, or causing to be made, a false statement to get a false claim paid;
- federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which, in addition to privacy protections applicable to healthcare providers and other entities, prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- the federal Food, Drug, and Cosmetic Act, or the FDCA, which among other things, strictly regulates drug marketing, prohibits manufacturers from marketing such products for off-label use and regulates the distribution of samples;
- federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs;
- the so-called “federal sunshine” law, which requires pharmaceutical and medical device companies to monitor and report certain financial interactions with certain healthcare providers and teaching hospitals to the Center for Medicare & Medicaid Services within the U.S. Department of Health and Human Services for re-disclosure to the public, as well as ownership and investment interests held by physicians, other healthcare providers and their immediate family members;
- state laws requiring pharmaceutical companies to comply with specific compliance standards, restrict financial interactions between pharmaceutical companies and healthcare providers or require pharmaceutical companies to report information related to payments to health care providers or marketing expenditures; and
- analogous state and foreign laws and regulations, such as state anti-bribery, anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

## ***Health care and other 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 2031, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, unless Congressional action is taken. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. 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, 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. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

In January 2021, a new executive order directed 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. In prior presidential administrations, several executive orders intended to lower the costs of prescription drug products were issued. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing a most favored nation model, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries effective January 1, 2021, but such final rule is subject to a nationwide preliminary injunction for its failure to comply with notice and comment rulemaking requirements. The current administration has frozen certain of the previous administration’s measures to reform drug prices, pending further review. Further, Executive Order 14063, signed on July 9, 2021, focuses on, among other things, the price of pharmaceuticals. To address these costs, the Order directs the Department of Health and Human Services, or HHS, to create a plan within 45 days to combat “excessive pricing of prescription drugs and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such drugs, and to address the recurrent problem of price gouging.”

On September 9, 2021, HHS released its plan to reduce drug prices. The key features of that plan are to: (a) make drug prices more affordable and equitable for all consumers and throughout the health care system by supporting drug price negotiations with manufacturers; (b) improve and promote competition throughout the prescription drug industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments. Further, on August 21, 2021, in response to the litigation challenging the most favored nation model, CMS issued a proposed rule to rescind the interim final rule, following public notice and comment. With issuance of this proposal, CMS stated that it will carefully consider the comments it received on the November 2020 interim final rule as it explores all options to incorporate value into payments for Medicare Part B drugs and improve beneficiaries’ access to evidence-based care.

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**

### ***Team members***

As of December 31, 2021, we had 341 team members employed with us full-time, of which 107 had a M.D. or Ph.D. degree. Of these team members, 234 were engaged in research and development activities, 13 were engaged in clinical activities, 32 were in technical operations and 62 were in general and administrative roles. None of our team members are represented by a labor union or covered by a collective bargaining agreement.

## ***Human capital strategy***

Our human capital strategy starts with our values:

- *A community of fearless innovators*
- *Rigorous and honest in our research*
- *Listening with open minds*
- *Committed to each other*

These values have helped us build a team that is focused on achieving our vision of providing life-long cures for patients suffering from serious diseases.

We believe the following priorities are key to realizing this vision:

### *Engagement*

We have a highly engaged team, and we regularly collect feedback to ensure their voices are heard. We do this through a combination of engagement surveys, weekly team meetings, one-on-one interactions, and open forums. In 2021, 98% of our team members participated in the Boston Globe's Top Places to Work survey. We have received this industry recognition for each of the last three years.

### *Total rewards (compensation and benefits)*

We are committed to rewarding our team members in order to continue to attract and retain talent. We do this by regularly conducting market assessments to ensure our compensation program is competitively positioned. We also engage our team members on a regular basis to understand what benefits they value. This feedback has allowed us to evolve our total rewards to respond proactively to the needs of our team.

### *Wellness*

In order to execute on our human capital strategy, the wellbeing of our team members comes first. To that end, we provide several benefits focused on the various physical, mental, and financial aspects of wellness. For example, in response to the COVID-19 pandemic, we implemented changes in our business to protect our team members and their families. These changes include flexible working schedules, weekly on-site testing, technology support and mandatory vaccination for all team members. As of December 31, 2021, all of our team members were in compliance with our COVID-19 vaccination policy.

### *Inclusion, diversity & belonging*

We continue to build an inclusive and diverse culture that allows for unique perspectives, creates an opportunity for all to grow and develop, and reflects the needs of relevant patient communities. Our Inclusion, Diversity and Belonging team develops monthly programs for our team members to engage with, hosts external speakers and panels, supports diverse local businesses, and creates communications for events that we honor throughout the year. In addition to our monthly programming, we are undertaking initiatives to accomplish the following goals, which were established with direct input from a company-wide listening tour and are linked to our values:

- Inclusion, Diversity and Belonging at Beam is a cultural priority with a clear vision, intentional commitment, and transparent accountability.
- We incorporate an Inclusion, Diversity and Belonging lens into our programs, policies, and processes, ensuring Beam team members understand how inclusion, diversity and belonging can have a positive effect on the employee experience.
- We take meaningful action to increase and support underrepresented talent, with specific emphasis on Black and Latinx team members.
- We honor and acknowledge various groups throughout the year, observing National Hispanic Heritage Month, Black History Month, International Women's Day, Global Diversity Awareness Month, and Indigenous People's Day.

## **Available Information**

Our website address is [www.beamtx.com](http://www.beamtx.com), and our investor relations website is located at [investors.beamtx.com](http://investors.beamtx.com). Information on our website is not incorporated by reference herein. We will make available on our website, free of charge, our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The SEC maintains an Internet site (<http://www.sec.gov>) containing reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC.

Investors and others should note that we announce material information to our investors using one or more of the following: SEC filings, press releases and our corporate website, including without limitation the “Investors Center” section of our website. We use these channels, as well as social media channels such as Twitter and LinkedIn, in order to achieve broad, non-exclusionary distribution of information to the public and for complying with our disclosure obligations under Regulation FD. It is possible that the information we post on our corporate website or other social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the “Investor Center” section of our corporate website and on our social media channels. The contents of our corporate website and social media channels are not, however, a part of this Annual Report on Form 10-K.

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

*You should carefully consider the risks and uncertainties described below together with all of the other information contained in this Annual Report on Form 10-K, including our consolidated financial statements and related notes appearing at the end of this Annual Report on Form 10-K, in evaluating our company. If any of the events or developments described below were to occur, our business, prospects, operating results and financial condition could suffer materially, the trading price of our common stock could decline. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently believe to be immaterial may also adversely affect our business.*

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

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

Since inception, we have incurred significant operating losses. Our net loss was \$370.6 million, \$194.6 million and \$78.3 million for the years ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2021, we had an accumulated deficit of \$768.3 million. We have financed our operations primarily through private placements of our preferred stock and proceeds from sales of our common stock. We have devoted all of our efforts to research and development. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if and as we:

- initiate clinical trials, including our BEACON-101 trial;
- continue our research programs and our preclinical development of other product candidates from our research programs;
- seek to identify additional research programs and additional product candidates;
- initiate preclinical testing and clinical trials for any other product candidates we identify and develop;
- maintain, expand, enforce, defend and protect our intellectual property portfolio and provide reimbursement of third-party expenses related to our patent portfolio;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- establish a sales, marketing, and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;
- further develop our platform;
- hire additional personnel, including research and development, clinical, and commercial personnel;
- add operational, financial, and management information systems and personnel, including personnel to support our product development;
- acquire or in-license products, intellectual property, medicines, and technologies;
- continue building and then maintain a commercial-scale cGMP manufacturing facility; and
- continue to operate as a public company.

We have not completed any clinical trials of any product candidates and expect that it will be many years, if ever, before we have a product candidate approved for commercialization. To become and remain profitable, we must develop and, either directly or through collaborators, eventually commercialize a medicine or medicines with significant market potential. This will require us to be successful in a range of challenging activities, including identifying product candidates, completing preclinical studies and clinical trials of product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing, and selling those medicines for which we may obtain marketing approval, 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 or large enough to achieve profitability. Because of the numerous risks and uncertainties associated with developing base editing product candidates, we are unable to predict the extent of any future losses or when we will become profitable, if at all. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business, or continue our operations.

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

We expect our expenses to increase in connection with our ongoing activities, particularly as we identify, continue the research and development of, initiate and continue clinical trials of, and seek marketing approval for, product candidates. In addition, if we obtain marketing approval for any product candidates we may develop, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing, and distribution to the extent that such sales, marketing, manufacturing, and distribution are not the responsibility of a collaborator. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce, or eliminate our research and product development programs or future commercialization efforts.

At December 31, 2021, our cash, cash equivalents, and marketable securities were \$965.6 million. We believe that our existing cash, cash equivalents, and marketable securities will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 months. However, our operating plan may change as a result of factors currently unknown to us, and we may need to seek additional funding sooner than planned. Our future capital requirements will depend on many factors, including:

- the cost of continuing to build our platform;
- the costs of acquiring licenses for the delivery modalities that will be used with our product candidates;
- the scope, progress, results, and costs of discovery, preclinical development, laboratory testing, manufacturing, and clinical trials for the product candidates we may develop;
- the costs of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims;
- the costs, timing, and outcome of regulatory review of the product candidates we may develop;
- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, distribution, coverage and reimbursement for any product candidates for which we receive regulatory approval to commercialize;
- the success of our license agreements and our collaborations;
- our ability to establish and maintain additional license agreements and collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any additional license agreements or collaboration agreements we obtain;
- the extent to which we acquire or in-license products, intellectual property and technologies;
- the costs of operating as a public company; and
- the costs of obtaining, building and expanding our internal manufacturing capacity.

Identifying potential product candidates and conducting preclinical studies 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 product candidates are approved, we may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of medicines that we do not expect to be commercially available for many years, if ever. 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 the attention of our management from their day-to-day activities, which may adversely affect our ability to develop and, if approved, commercialize our product candidates. We cannot be certain that additional funding will be available to us 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 on a timely basis, we may have to significantly delay, scale back or discontinue the development or, if approved, commercialization of our product candidates or other research and development initiatives. Our current and any future license agreements and collaboration agreements may also be terminated if we are unable to meet the payment or other obligations under the agreements. 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 also 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 we may develop.***

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 licensing arrangements. We do not have any committed external source of capital. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted. The terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, declaring dividends, and possibly other restrictions.

If we raise funds through additional 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 we may develop, or we may have to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce, or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. In addition, we have and may in the future enter collaboration and acquisition agreements, pursuant to which we are required to issue additional shares of our common stock in connection with future milestone payment obligations. These and other future issuances to our partners and collaborators may cause substantial dilution to our stockholders.

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

We are an early-stage company. We were founded in January 2017 and began operations in July 2017. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our platform and technology, identifying potential product candidates, undertaking preclinical studies and preparing for the initiation of clinical trials. Nearly all of our product development programs are still in the preclinical or research stage of development, and their risk of failure is high. We have not yet demonstrated an ability to initiate or successfully complete any clinical trials, including large-scale, pivotal clinical trials, obtain marketing approvals, manufacture a commercial-scale medicine, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Typically, it takes about 10 to 15 years to develop a new medicine from the time it is discovered to when it is available for treating patients. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

Our limited operating history, particularly in light of the rapidly evolving base editing and gene editing field, may make it difficult to evaluate our technology and industry and predict our future performance. Our short 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 a new business, we may encounter other unforeseen expenses, difficulties, complications, delays, and other known and unknown factors. We will eventually need to transition from a company with a research focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

***We have never generated revenue from product sales and may never become profitable.***

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

- identify product candidates and complete research and preclinical and clinical development of the product candidates we or our collaborators may identify;
- seek and obtain regulatory and marketing approvals for any of our product candidates for which we or our collaborators successfully complete clinical trials;
- launch and commercialize any of our product candidates for which we obtain regulatory and marketing approval by establishing a sales force, marketing, and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- qualify for adequate coverage and reimbursement by government and third-party payors for our product candidates for which we or our collaborators obtain regulatory and marketing approval;
- develop, maintain, and enhance a sustainable, scalable, reproducible, and transferable manufacturing process for the product candidates we or our collaborators may develop;
- manufacture materials in compliance with cGMP and establish the infrastructure necessary to support and develop large-scale manufacturing capabilities;
- establish and maintain supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products, and services to support clinical development and the market demand for our product candidates for which we or our collaborators obtain regulatory and marketing approval;
- obtain market acceptance of any product candidates we or our collaborators may develop as viable treatment options;
- address competing technological and market developments;
- implement internal systems and infrastructure, as needed;
- negotiate favorable terms in any collaboration, licensing, or other arrangements into which we may enter and performing our obligations in such collaborations, licensing or other arrangements;
- maintain, protect, enforce, defend, and expand our portfolio of intellectual property rights, including patents, trade secrets, and know-how;
- avoid and defend against third-party interference, infringement, and other intellectual property claims; and
- attract, hire, and retain qualified personnel.

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

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

***Our future ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.***

We have incurred substantial losses during our history, and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset a portion of future taxable income, if any, subject to expiration of such carryforwards in the case of carryforwards generated prior to 2018. Additionally, we continue to generate business tax credits, including research and development tax credits, which generally may be carried forward to offset a portion of future taxable income, if any, subject to expiration of such credit carryforwards. In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an “ownership change,” generally defined as one or more shareholders or groups of shareholders who own at least 5% of the corporation’s equity increasing their ownership in the aggregate by a greater than 50 percentage point change (by value) in their equity ownership over a three-year period, the corporation’s ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research and development tax credits) to offset its post-change income or taxes may be limited. The amount of the annual limitation is determined based on the value of the corporation immediately prior to the ownership change. Our prior equity offerings and other changes in our stock ownership may have resulted in such ownership changes. In addition, we may experience ownership changes in the future as a result of shifts in our stock ownership, some of which are outside of our control. As a result, if we earn net taxable income, our ability to use our pre-change NOLs or other pre-change tax attributes to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. Additional limitations on our ability to utilize our NOLs to offset future taxable income may arise as a result of our corporate structure, whereby NOLs generated by certain of our subsidiaries or controlled entities may not be available to offset taxable income earned by our subsidiaries or other controlled entities. In addition, under legislation commonly referred to as the Tax Cuts and Jobs Act of 2017, or the Tax Act, as amended by the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, the amount of post-2017 NOLs that we are permitted to deduct in any taxable year is limited to 80% of our taxable income in such year. The Tax Act generally eliminates the ability to carry back any NOLs to prior taxable years, while allowing post-2017 unused NOLs to be carried forward indefinitely. There is a risk that due to changes under the Tax Act, regulatory changes, or other unforeseen reasons, our existing NOLs or business tax credits could expire or otherwise be unavailable to offset future income tax liabilities. At the state level, there may also be periods during which the use of NOLs or business tax credits is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. For these reasons, we may not be able to realize a tax benefit from the use of our NOLs or tax credits, even if we attain profitability.

**Risks related to discovery, development, and commercialization**

***Base editing is a novel technology that is not yet clinically validated for human therapeutic use. The approaches we are taking to discover and develop novel therapeutics are unproven and may never lead to marketable products.***

We are focused on developing potentially curative medicines utilizing base editing technology. Although there have been significant advances in the field of gene therapy, which typically involves introducing a copy of a gene into a patient’s cell, and gene editing in recent years, base editing technologies are new and largely unproven. The technologies that we have licensed and that we intend to develop and intend to license have not yet completed any clinical trials, nor are we aware of any clinical trials for safety or efficacy having been completed by third parties using our base editing or similar technologies. The scientific evidence to support the feasibility of developing product candidates based on these technologies is both preliminary and limited, and base editing and delivery modalities for it are novel. Successful development of product candidates by us will require solving a number of issues, including safely delivering a therapeutic into target cells within the human body or in an *ex vivo* setting, optimizing the efficiency and specificity of such product candidates, and ensuring the therapeutic selectivity of such product candidates. Several biological steps are required for delivery of base editing medicines to translate into therapeutically active medicines. These processing steps may differ between individuals and differ based on the targeted tissue. These differences could lead to variable levels of therapeutic protein, variable activity, immunogenicity, or variable distribution to tissues further increasing the risk inherent in the development of base editing medicines. There can be no assurance we will be successful in solving any or all of these issues, or that we will be able to progress our preclinical studies or clinical trials in accordance with anticipated timelines.

We have concentrated our research efforts to date on preclinical work to bring therapeutics to the clinic for our initial indications, and our future success is highly dependent on the successful development of base editing technologies, cellular delivery methods and therapeutic applications of that technology. While some of the existing gene editing technologies have progressed to clinical trials, they continue to suffer from various limitations, and such limitations may affect our future success. We may decide to alter or abandon our initial programs as new data become available and we gain experience in developing base editing therapeutics. We cannot be sure that our technologies will yield satisfactory products that are safe and effective, scalable or profitable in our initial indications or any other indication we pursue.

Development activities in the field of base editing are currently subject to a number of risks related to the ownership and use of certain intellectual property rights that are subject to patent interference proceedings in the United States and opposition proceedings in Europe. For additional information regarding the risks that may apply to our and our licensors’ intellectual property rights, see the section entitled “—Risks related to our intellectual property”.



***We may not be successful in our efforts to identify and develop potential product candidates. If these efforts are unsuccessful, we may never become a commercial stage company or generate any revenues.***

The success of our business depends primarily upon our ability to identify, develop, and commercialize product candidates based on our gene editing platform. Nearly 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 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 base editing will position us to rapidly expand our portfolio of product candidates beyond our current product candidates we may develop after only minimal changes to the product candidate construct, we have not yet successfully developed any product candidate and our ability to expand our portfolio may never materialize.

If any of these events occur, we may be forced to abandon our research or development efforts for a program or programs, which would have a material adverse effect on our business, financial condition, results of operations, and prospects. Research programs to identify new product candidates require substantial technical, financial, and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful, which would be costly and time-consuming.

***The gene editing field is relatively new and is evolving rapidly. We are focusing our research and development efforts primarily on gene editing using base editing technology, but other gene editing technologies may be discovered that provide significant advantages over base editing, which could materially harm our business.***

We focus our research and development efforts primarily on gene editing technologies using base editing. Other companies have previously undertaken research and development of gene editing technologies using zinc finger nucleases, engineered meganucleases, and transcription activator-like effector nucleases, or TALENs, but to date no company has obtained marketing approval for a product candidate developed using those technologies. There can be no certainty that base editing technology will lead to the development of genetic medicines or that other gene editing technologies will not be considered better or more attractive for the development of medicines. For example, Feng Zhang's group at MIT and Broad Institute, and, separately, Samuel Sternberg's group at Columbia University announced the discovery of the use of transposons, or jumping genes, in June 2019. Transposons can insert themselves into different places in the genome and can be programmed to carry specific DNA sequences to specific sites, without the need for making double-stranded breaks in DNA. In addition, one of our founders, David Liu, and his group at Broad Institute developed a novel gene editing technology. We have secured an exclusive license from Prime Medicine, a company founded by David Liu, to pursue this new technology in certain fields and for certain applications similar to those we are already pursuing with base editing. Our license does not cover all fields and applications of this new technology for gene editing and Prime Medicine retains broad rights to use this technology outside of the fields licensed to us. It is possible that this gene editing technology developed by David Liu's group is competitive with our business, and it is also possible that such gene editing technology may potentially be considered more attractive than base editing. Therefore, Prime Medicine may pursue this technology in other fields and for other applications and may develop competing products using such technology. David Liu has reported results from his lab related to base editing in mitochondria; this is accomplished by splitting the deaminase into two halves, which are reassembled at the desired regions of the mitochondrial DNA. This new technology could be used to treat mitochondrial diseases. Our current technology cannot edit within the mitochondria. In addition, Geoffrey von Maltzahn and others have launched a company called Tessera Therapeutics, Inc., which is focused on a technology they call "Gene Writing." This technology, which utilizes mobile genetic elements, can alter the genome by inserting genes and exons, introducing small insertions and deletions, or by changing single or multiple DNA base pairs. Similarly, another new gene editing technology that has not been discovered yet may be determined to be more attractive than base editing. Moreover, if we decide to focus primarily on gene editing technologies other than those involving base editing, we cannot be certain we will be able to obtain rights to such technologies. Although all of our founders who currently provide consulting and advisory services to us in the area of base editing technologies have assignment of inventions obligations to us with respect to the services they perform for us, these assignment of inventions obligations are subject to limitations and do not extend to their work in other fields or to the intellectual property arising from their employment with their respective academic and research institutions. To obtain intellectual property rights assigned by these founders to such institutions, we would need to enter into license agreements with such institutions, which may not be available on commercially reasonable terms or at all. Further, while our three founders have non-competition clauses in their respective consulting agreements, the non-competition obligation is limited to the field of base editing for human therapeutics, and our founders have developed and may in the future develop new technologies that are outside of the field of their non-competition obligations but may be competitive to our business. For example, as discussed above, David Liu and his group at Broad Institute have developed novel gene editing technology outside of the field of his non-competition obligations that may be used to develop products that compete with our business. Any of these factors could reduce or eliminate our commercial opportunity, and could have a material adverse effect on our business, financial condition, results of operations, and prospects.

***We are very early in our development efforts. Nearly all of our product candidates are still in preclinical development or earlier stages and it will be many years before we or our collaborators commercialize a product candidate, if ever. If we are unable to advance our product candidates to and through 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 are very early in our development efforts and have focused our research and development efforts to date on base editing and delivery technology, identifying our initial targeted disease indications and product candidates in these indications. Our future success depends heavily on the successful development of our base editing product candidates. With the exception of our BEACON-101 clinical trial to evaluate the safety and efficacy of BEAM-101 for the treatment of sickle cell disease, all of our product candidates are in preclinical development or in discovery. We have invested substantially all of our efforts and financial resources in building our base editing and delivery technologies, and the identification and preclinical development of our current product candidates. 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, if approved, 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 FDA of our INDs 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 for our BEACON-101 trial or other clinical trials we may seek to conduct, the start or progress of such 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 our clinical trial or change their position on the acceptability of our data, trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials or impose stricter requirements for approval than we currently expect. There are equivalent processes and risks applicable to clinical trial applications in other countries, including in Europe.

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

- sufficiency of our financial and other resources to complete the necessary preclinical studies, IND-enabling studies, and clinical trials;
- regulatory clearance of IND applications or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for our product candidates;
- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishment of arrangements with third-party manufacturers for clinical supply and commercial manufacturing and, where applicable, commercial manufacturing capabilities;
- successful development of our internal manufacturing processes and transfer to larger-scale facilities operated by either a CMO, or by us;
- obtaining and maintaining patent, trade secret, and other intellectual property protection and non-patent exclusivity for our medicines;
- launching commercial sales of the medicines, if and when approved, whether alone or in collaboration with others;
- acceptance of the products, if and when approved, by patients, the medical community, and third-party payors;
- effectively competing with other therapies and treatment options;
- a continued acceptable safety profile of the medicines following approval;
- enforcing and defending intellectual property and proprietary rights and claims; and
- supplying the product at a price that is acceptable to the pricing or reimbursement authorities in different countries.

If we do not successfully achieve one or more of these activities 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 do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

***If any of the product candidates we may develop, or the delivery modalities we rely on to administer them, cause serious adverse events, undesirable side effects, or unexpected characteristics, such events, side effects or characteristics could delay or prevent regulatory approval of the product candidates, 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 gene editing technologies and none involving base editing technology similar to our technology. It is impossible to predict when or if any product candidates we 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, serious blood disorders and death. There can be no assurance that base editing technologies, or components of our product candidates or methods of delivery, will not cause undesirable side effects, as improper editing of a patient's DNA and other effects could lead to lymphoma, leukemia, or other cancers, other serious conditions or syndromes or other aberrantly functioning cells.

A significant risk in any base editing product candidate is that "off-target" edits may occur, which could cause serious adverse events, undesirable side effects or unexpected characteristics. For example, Erwei Zuo et al. reported that cytosine base editors generated substantial off-target edits, that is, edits in unintended locations on the DNA, when tested in mouse embryos. Such unintended edits are referred to as "spurious deamination." We cannot be certain that off-target editing will not occur in any of our planned or future clinical studies, and the lack of observed side effects in preclinical studies does not guarantee that such side effects will not occur in human clinical studies. We have developed assays that can detect off-target edits, even when such edits occur at very low frequencies. Using these assays, we have observed off-target edits in our base editing product candidates. As the sensitivity of these assays increases, it is possible that we will continue to detect more such off-target edits. While we do not believe that the off-target edits we have observed to date have had a material adverse impact on the safety or benefit of our product candidates, if, in the future, we detect off-target edits for a product candidate that negatively impact safety or efficacy, our ability to develop the product candidate as a therapeutic could be adversely affected. There is also the potential risk of delayed adverse events following exposure to base editing therapy due to the permanence of edits to DNA or due to other components of product candidates used to carry the genetic material. Further, because base editing makes a permanent change, the therapy cannot be withdrawn, even after a side effect is observed. In addition, Rees et al. and Grunewald et al. have reported that the deaminases we currently use in our C base editors and our A base editors for use in DNA base editing also cause unintended mutations in RNA for as long as the editor is present in the cell.

Although we and others have demonstrated the ability to engineer base editors to improve the specificity of their edits in a laboratory setting, we cannot be sure that our engineering efforts will be effective in any product candidates that we may develop. For example, we might not be able to engineer an editor to make the desired change or a by-stander edit could diminish the effectiveness of an edit that we make.

In certain rare DNA sequence contexts, where more than one edit occurs on a contiguous piece of DNA, the repair of two or more nicks may lead to a deletion. For example, in our BEAM-101 program, where we are simultaneously editing two positions in the promoters of the HBG2 and HBG1 genes, which share >99% sequence identity and are contiguous due to a gene duplication event, we observed a 5 kb deletion in HBG2 at single digit percentages in animal studies. We do not believe that such a deletion represents a safety or efficacy concern because healthy individuals, including those with hereditary persistence of fetal hemoglobin, with naturally-occurring deletions at this locus, including some as large as 13 kb, have been documented. However, if we were to observe deletions that have a negative effect on HbF upregulation or on other important cellular attributes, our ability to develop BEAM-101 as a therapeutic could be adversely affected.

In certain of our programs, we plan to use LNPs to deliver our base editors. LNPs have been shown to induce oxidative stress in the liver at certain doses, as well as initiate systemic inflammatory responses that can be fatal in some cases. While we aim to continue to optimize our LNPs, there can be no assurance that our LNPs will not have undesired effects. Our LNPs could contribute, in whole or in part, to one or more of the following: immune reactions; infusion reactions; complement reactions; opsonization reactions; antibody reactions including IgA, IgM, IgE or IgG or some combination thereof; or reactions to the PEG from some lipids or PEG otherwise associated with the LNP. Certain aspects of our investigational medicines may induce immune reactions from either the mRNA or the lipid as well as adverse reactions within liver pathways or degradation of the mRNA or the LNP, 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 legacy LNPs. 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.

Our viral vectors that we plan to use in certain of our base editing programs, including AAV or lentiviruses, which are relatively new approaches used for disease treatment, also have known side effects, and for which additional risks could develop in the future. In past clinical trials that were conducted by others with non-AAV viral vectors, several significant side effects were caused by gene therapy treatments, including reported cases of leukemia and death. For example, in February 2021, bluebird bio reported a suspected unexpected serious adverse reaction, or SUSAR, of acute myeloid leukemia, and a SUSAR of myelodysplastic syndrome in its Phase 1/2 clinical trial of LentiGlobin, a gene therapy using a lentiviral vector for the treatment of sickle cell disease, which resulted in the FDA placing a clinical hold on the trial and the suspension of the conditional marketing authorization by the EMA of ZYNTEGLO (beti-cel), which also uses a lentiviral vector, for patients 12 years and older with transfusion-dependent beta thalassemia who do not have a  $\beta^0/\beta^0$  genotype, for whom HSC transplantation is appropriate, but HLA related HSC donor is not available. Other potential side effects of viral vectors could include an immunologic reaction and insertional oncogenesis, which is the process whereby the insertion of a functional gene near a gene that is important in cell growth or division results in uncontrolled cell division, which could potentially enhance the risk of malignant transformation. If the vectors we use demonstrate a similar side effect, or other adverse events, we may be required to halt or delay further clinical development of any potential product candidates using such technology. Furthermore, the FDA has stated that lentiviral vectors possess characteristics that may pose high risks of delayed adverse events. Such delayed adverse events may occur in other viral vectors, including AAV vectors, at a lower rate.

In addition to side effects and adverse events caused by our product candidates, the conditioning administration process or related procedures which may be used in our electroporation pipeline also can cause adverse side effects and adverse events. Additionally, we have and may continue to collaborate with third parties to develop alternative conditioning regimens, including, for example, our collaboration with Magenta, and we are conducting our own research into novel conditioning strategies. We cannot predict if alternative conditioning regimens will be compatible with our product candidates. If in the future we are unable to demonstrate that such adverse events were not caused by the conditioning regimens used, or administration process or related procedure, the FDA, the European Commission, EMA or other regulatory authorities could order us to cease further development of, or deny or limit approval of, our product candidates using such regimens, processes or procedures for any or all target indications. Even if we are able to demonstrate that adverse events are not related to the product candidate or the administration of such product candidate, such occurrences could affect patient recruitment, the ability of enrolled patients to complete the clinical trial, or the commercial viability of any product candidates that obtain regulatory approval.

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 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 any of the above adverse events were caused by factors other than our product candidate, the FDA, the EMA or other regulatory authorities could order us to cease further development of, or deny approval of, any product candidates we are able to develop for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any product candidate we may develop, 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 identify and develop product candidates, and may harm our business, financial condition, result of operations, and prospects significantly.

Additionally, if we successfully develop a product candidate and it receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits of treatment with such product candidate outweigh the risks for each potential patient, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, extensive patient monitoring, or distribution systems and processes that are highly controlled, restrictive, and more costly than what is typical for the industry. Furthermore, if we or others later identify undesirable side effects caused by any product candidate that we develop, 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 or limit the approved use of such product candidate;
- we may be required to conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of any product candidates we may identify and develop and could have a material adverse effect on our business, financial condition, and results of operations.

***We have not tested any of our proposed delivery modalities and product candidates in clinical trials and any favorable preclinical results are not predictive of results that may be observed in clinical trials.***

We have not tested any of our proposed delivery modalities in clinical trials. For example, in certain of our base editing programs we intend to use novel split intein technology for AAV gene therapy that we believe will allow us to deliver the base editor and guide RNA construct by co-infection with two viruses, where each virus contains one half of the editor. The scientific evidence to support the feasibility of developing product candidates based on this technology is both preliminary and limited. We also intend to use LNPs to deliver some of our base editors. While LNPs have been used to deliver smaller molecules, such as RNAi, they have not been clinically proven to deliver larger RNA molecules, such as the ones we intend to use for our base editors. Furthermore, as with many AAV-mediated gene therapy approaches, certain clinical trial patients' immune systems might prohibit the successful delivery, thereby potentially limiting treatment outcomes of these patients. Even if initial clinical trials in any of our product candidates are successful, these product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through preclinical studies and initial clinical trials.

There is a high failure rate for drugs and biologics proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later stage clinical trials even after achieving promising results in earlier stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit, or prevent regulatory approval. In addition, regulatory delays or rejections may be encountered as a result of many factors, including changes in regulatory policy during the period of product development.

Any such adverse events may cause us to delay, limit, or terminate planned clinical trials, any of which would have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, the results of preclinical studies or clinical trials may not be predictive of the results of later preclinical studies or clinical trials. 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 product candidates.

***If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.***

We or our collaborators may not be able to initiate or continue clinical trials for any product candidates we identify or develop if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA, the EMA or other analogous regulatory authorities outside the United States, or as needed to provide appropriate statistical power for a given trial. Enrollment may be particularly challenging for some of the rare genetically defined diseases we are targeting in our most advanced programs, as well as for some of our product candidates for pediatric populations, and delays related to the COVID-19 pandemic could exacerbate delays in enrolling for new clinical trials. In addition, if patients are unwilling to participate in our base editing trials because of negative publicity from adverse events related to the biotechnology, gene therapy, or gene editing fields, competitive clinical trials for similar patient populations, clinical trials in competing products, or for other reasons, the timeline for recruiting patients, conducting studies, and obtaining regulatory approval of any product candidates we may develop may be delayed. Moreover, some of our competitors currently and may in the future have ongoing clinical trials for product candidates that treat the same indications as product candidates we are developing and may develop in the future, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.

Clinical trial patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- size of the patient population and process for identifying patients;
- design of the trial protocol;
- availability and efficacy of approved medications for the disease under investigation;
- availability of genetic testing for potential patients;
- ability to obtain and maintain patient informed consent;
- risk that enrolled patients will drop out before completion of the trial;
- eligibility and exclusion criteria for the trial in question;
- perceived risks and benefits of the product candidate under trial;

- perceived risks and benefits of base editing as a therapeutic approach;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients, especially for those conditions which have small patient pools.

Our ability to successfully initiate, enroll, and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- different standard-of-care for patients with a particular disease;
- difficulty in locating qualified local consultants, physicians, and partners; and
- potential burden of complying with a variety of foreign laws, medical standards, and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment and of gene editing technologies.

Enrollment delays in our clinical trials may result in increased development costs for any product candidates we may develop, which would cause the value of our company to decline and limit our ability to obtain additional financing. If we or our collaborators have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit, or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations, and prospects.

***If clinical trials of any product candidates we identify and develop fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of such product candidates.***

Before obtaining marketing approval from regulatory authorities for the sale of any product candidates we identify and develop, we must complete preclinical development and then conduct extensive clinical trials to demonstrate their safety and efficacy in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete, and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results.

Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses. 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 product candidates.

We and our collaborators may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize any product candidates we identify and develop, including:

- delays in reaching a consensus with regulators on trial design and endpoints;
- regulators, institutional review boards, or IRBs, or independent ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- delays in reaching or failing to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective CROs and clinical trial sites;
- clinical trials of any product candidates we may develop may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development or research programs;
- difficulty in designing well-controlled clinical trials due to ethical considerations which may render it inappropriate to conduct a trial with a control arm that can be effectively compared to a treatment arm;
- difficulty in designing clinical trials and selecting endpoints for diseases that have not been well-studied and for which the natural history and course of the disease is poorly understood;

- the number of patients required for clinical trials of any product candidates we develop may be larger than we anticipate; enrollment of suitable participants in these clinical trials, which may be particularly challenging for some of the rare genetically defined diseases we are targeting in our most advanced programs, may be delayed or slower than we anticipate; or patients may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators, IRBs, or independent ethics committees may require that we or our investigators suspend or terminate clinical research or clinical trials of any product candidates we develop for various reasons, including noncompliance with regulatory requirements, a finding of undesirable side effects or other unexpected characteristics, or that the participants are being exposed to unacceptable health risks or after an inspection of our clinical trial operations or trial sites;
- the cost of clinical trials of any product candidates we may develop may be greater than we anticipate;
- the supply or quality of any product candidates we may develop or other materials necessary to conduct clinical trials of any product candidates we develop may be insufficient or inadequate, including as a result of delays in the testing, validation, manufacturing, and delivery of any product candidates we may develop to the clinical sites by us or 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 dropping out of a trial;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- occurrence of serious adverse events associated with any product candidates we may develop that are viewed to outweigh their potential benefits;
- occurrence of serious adverse events in trials of the same class of agents conducted by other sponsors;
- disruption to the operations of the FDA; and
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols or otherwise complying with additional requirements.

If we or our collaborators are required to conduct additional clinical trials or other testing of any product candidates we develop beyond those that we currently contemplate, if we or our collaborators are unable to successfully complete clinical trials or other testing of any product candidates we develop, or if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we or our collaborators may:

- be delayed in obtaining marketing approval for any such product candidates we may develop or not obtain marketing approval 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, including boxed 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 REMS or through modification to an existing REMS;
- be sued; or
- experience damage to our reputation.

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

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

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications 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. 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.

***Even if we complete the necessary clinical trials, we cannot predict when, or if, we will obtain regulatory approval to commercialize a product candidate we develop in the United States or any other jurisdiction, and any such approval may be for a more narrow indication than we seek.***

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if any product candidates we may develop meet their safety and efficacy endpoints in clinical trials, the regulatory authorities may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials, and the review process.

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

Marketing approval by the FDA in the United States, if obtained, does not ensure approval by regulatory authorities in other countries or jurisdictions. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country. Approval processes vary among countries and can involve additional product candidate testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and costs for us and require additional preclinical studies or clinical trials which could be costly and time-consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our product candidates we may develop in those countries. The foreign regulatory approval process involves all of the risks associated with FDA approval. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of our product candidates will be unrealized.

***Even if any product candidates we may develop receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors, and others in the medical community necessary for commercial success.***

The commercial success of any of our product candidates we may develop will depend upon its degree of market acceptance by physicians, patients, third-party payors, and others in the medical community. Ethical, social, and legal concerns about genetic medicines generally and base editing technologies specifically could result in additional regulations restricting or prohibiting the marketing of our product candidates we may develop. Even if any product candidates we may develop receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors, and others in the medical community. 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 and perceived advantages compared to alternative treatments;
- the limitation to our targeted patient population and limitations or warnings contained in approved labeling by the FDA or other regulatory authorities;



- the ability to offer our medicines for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the clinical indications for which the product candidate is approved by the FDA, the EMA, or other regulatory agencies;
- public attitudes regarding genetic medicine generally and gene editing and base editing technologies specifically;
- the willingness of the target patient population to try novel therapies and of physicians to prescribe these therapies, as well as their willingness to accept a therapeutic intervention that involves the editing of the patient's gene;
- product labeling or product insert requirements of the FDA, the EMA, or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

Even if any of our product candidates we may develop are approved, such products may not achieve an adequate level of acceptance, we may not generate significant product revenues, and we may not become profitable.

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

We do not have a sales or marketing infrastructure and do not have experience in the sale, marketing, or distribution of pharmaceutical products. To achieve commercial success for any approved medicine for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to third parties. In the future, we may choose to build a focused sales, marketing, and commercial support infrastructure to sell, or participate in sales activities with our collaborators for, some of our product candidates we develop if and when they are approved.

There are risks involved with both establishing our own commercial capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force or reimbursement specialists 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 and other commercialization capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our commercialization personnel.

Factors that may inhibit our efforts to commercialize our product candidates we may develop on our own include:

- our inability to recruit and retain adequate numbers of effective sales, marketing, reimbursement, customer service, medical affairs, and other support personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines;
- the inability of reimbursement professionals to negotiate arrangements for formulary access, reimbursement, and other acceptance by payors;
- restricted or closed distribution channels that make it difficult to distribute our product candidates we may develop to segments of the patient population;
- the lack of complementary medicines 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 commercialization organization.

If we enter into arrangements with third parties to perform sales, marketing, commercial support, and distribution services, our product revenues or the profitability of these product revenues to us may be lower than if we were to market and sell any medicines we may develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to commercialize our product candidates we may develop or may be unable to do so on terms that are favorable to us. We may 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 medicines effectively. If we do not establish commercialization capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates we may develop.

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

The development and commercialization of new drug products is highly competitive. Moreover, the base editing and delivery technology fields are characterized by rapidly changing technologies, significant competition, and a strong emphasis on intellectual property. We will face competition with respect to any product candidates that we may seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. 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 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 the disease indications for which we have 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.

There are several other companies utilizing CRISPR/Cas9 nuclease technology, including Caribou Biosciences, Editas Medicine, CRISPR Therapeutics, Intellia Therapeutics, Arbor Biotechnologies, Metagenomi, and Mammoth Biosciences. Several additional companies utilize other nuclease-based gene editing technologies, including Zinc Fingers, Arcuses, and TAL Nucleases, which includes Sangamo Biosciences, Precision BioSciences, bluebird bio, Allogene Therapeutics, and Collectis. Additionally, newer gene editing modalities are emerging, including from Prime Medicine, Tessera Therapeutics, Shape Therapeutics, Scribe Therapeutics, Korro Bio, PerkinElmer (formerly Horizon Discovery) and Intellia Therapeutics. PerkinElmer and Intellia Therapeutics are developing base editing technology and Tessera Therapeutics is utilizing mobile genetic elements for gene editing. In addition, we face competition from companies utilizing various gene therapy, oligonucleotides, and CAR-T therapeutic approaches.

Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future that are approved to treat the same diseases for which we may obtain approval for our product candidates we may develop. This may include other types of therapies, such as small molecule, antibody, and/or protein therapies.

Many of our current or potential competitors, either alone or with their collaboration partners, may 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. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize product candidates that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any product candidates that we may develop or that would render any product candidates that we may develop obsolete or non-competitive. Our competitors also may obtain FDA or other regulatory approval for their product candidates more rapidly than we may obtain approval for ours, 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.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any product candidates that we may develop and commercialize.

***Adverse public perception of genetic medicines, and gene editing and base editing in particular, may negatively impact regulatory approval of, and/or demand for, our potential products.***

Our potential therapeutic products involve editing the human genome. The clinical and commercial success of our potential products will depend in part on public understanding and acceptance of the use of gene editing therapy for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene editing is unsafe, unethical, or immoral, and, consequently, our product candidates may not gain the acceptance of the public or the medical community. For example, a public backlash developed against gene therapy following the death of a patient in 1999 during a gene therapy clinical trial. The death of the clinical trial subject was due to complications related to AAV vector administration. In addition, in 2020, three patients in Audentes Therapeutics' clinical trial investigating AT132 (a gene therapy product candidate which was being delivered via AAV administration) for X-linked myotubular myopathy (XLMTM) died. The immediate cause of death in two cases was sepsis and in a third case was gastrointestinal bleeding, each of which followed progressive liver dysfunction that occurred within the first 4-6 weeks following AT132 dosing, and which did not respond to standard treatment. 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.

In addition, gene editing technology is subject to public debate and heightened regulatory scrutiny due to ethical concerns relating to the application of gene editing technology to human embryos or the human germline. For example, academic scientists in several countries, including the United States, have reported on their attempts to edit the gene of human embryos as part of basic research. In addition, in November 2018, Dr. Jiankui He, a Chinese biophysics researcher who was an associate professor in the Department of Biology of the Southern University of Science and Technology in Shenzhen, China, reportedly claimed he had created the first human genetically edited babies, twin girls. This claim, and another that Dr. He had helped create a second gene-edited pregnancy, was subsequently confirmed by Chinese authorities and was negatively received by the public, in particular those in the scientific community. News reports indicate that Dr. He was sentenced to three years in prison and fined \$430,000 in December 2019 by the Chinese government for illegal medical practice in connection with such activities. In the wake of the claim, the World Health Organization established a new advisory committee to create global governance and oversight standards for human gene editing and announced plans for a new global registry to track research on human gene editing. The Alliance for Regenerative Medicine also released principles for the use of gene editing in therapeutic applications endorsed by a number of companies that use gene editing technologies.

Regulation of gene editing technology varies across jurisdictions. In the United States, germline editing for clinical application has been expressly prohibited since enactment of a December 2015 FDA ban on such activity. Prohibitions are also in place in the U.K., across most of Europe, in China, and many other countries around the world. In the United States, the NIH has announced that the agency would not fund any use of gene editing technologies in human embryos, noting that there are multiple existing legislative and regulatory prohibitions against such work, including the Dickey-Wicker Amendment, which prohibits the use of appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. Laws in the U.K. prohibit genetically modified embryos from being implanted into women, except that mitochondrial replacement therapy has been permitted in the U.K. since 2016. Separately, embryos can be altered in the U.K. in research labs under license from the Human Fertilisation and Embryology Authority. Research on embryos is more tightly controlled in some other European countries.

Moreover, in an annual worldwide threat assessment report delivered to the U.S. Congress in February 2016, the U.S. Director of National Intelligence stated that research into gene editing that is conducted under different regulatory standards than those of Western countries probably increases the risk of the creation of potentially harmful biological agents or products, including weapons of mass destruction. He noted that given the broad distribution, low cost, and accelerated pace of development of gene editing technology, its deliberate or unintentional misuse could have far-reaching economic and national security implications.

Although we do not use our technologies to edit human embryos or the human germline, such public debate about the use of gene editing technologies in human embryos and heightened regulatory scrutiny could prevent or delay our development of product candidates. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair our development and commercialization of product candidates or demand for any product candidates we may develop. Adverse events in our preclinical studies or clinical trials or those of our competitors or of academic researchers utilizing gene editing technologies, even if not ultimately attributable to product candidates we may identify and develop, and the gene publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of potential product candidates we may identify and develop, stricter labeling requirements for those product candidates that are approved, and a decrease in demand for any such product candidates. Use of gene editing technology by a third party or government to develop biological agents or products that threaten U.S. national security could similarly result in such negative impacts to us.

***Even if we are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations, third-party reimbursement practices, or healthcare reform initiatives, which would harm our business.***

The regulations that govern marketing approvals, pricing, and reimbursement for new medicines vary widely from country to country. Some countries require approval of the sale price of a medicine before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a medicine in a particular country, but then be subject to price regulations that delay or might even prevent our commercial launch of the medicine, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the medicine in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates we may develop, even if any product candidates we may develop obtain marketing approval.

Our ability to commercialize any medicines successfully also will depend in part on the extent to which reimbursement for these medicines and related treatments will be available from government authorities or healthcare program, private health plans, and other organizations. Government authorities and third-party payors, such as private health plans, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are challenging the prices charged for medical products and requiring that drug companies provide them with predetermined discounts from list prices. Novel medical products, if covered at all, may be subject to enhanced utilization management controls designed to ensure that the products are used only when medically necessary. Such utilization management controls may discourage the prescription or use of a medical product by increasing the administrative burden associated with its prescription or creating coverage uncertainties for prescribers and patients. We cannot be sure that reimbursement will be available for any medicine that we commercialize and, if reimbursement is available, that the level of reimbursement will be adequate. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved medicines, and coverage may be more limited than the purposes for which the medicine is approved by the FDA, the EMA or other regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any medicine will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for new medicines, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the medicine and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost medicines and may be incorporated into existing payments for other services. Net prices for medicines may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of medicines from countries where they may be sold at lower prices than in the United States. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved medicines we may develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize medicines, and our overall financial condition.

***Due to the novel nature of our technology and the potential for any product candidates we may develop to offer therapeutic benefit in a single administration or limited number of administrations, we face uncertainty related to pricing and reimbursement for these product candidates.***

Our initial target patient populations are relatively small, as a result of which the pricing and reimbursement of any product candidates we may develop, if approved, must be adequate to support the necessary commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell any such product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to any product candidates we may develop (e.g., for administration of our product candidate to patients) is also important. Inadequate reimbursement for such services may lead to physician and payor resistance and adversely affect our ability to market or sell our product candidates we may develop. In addition, we may need to develop new reimbursement models in order to realize adequate value. Payors may not be able or willing to adopt such new models, and patients may be unable to afford that portion of the cost that such models may require them to bear. If we determine such new models are necessary but we are unsuccessful in developing them, or if such models are not adopted by payors, our business, financial condition, results of operations, and prospects could be adversely affected.

We expect the cost of a single administration of genetic medicines, such as those we are seeking to develop, to be substantial, when and if they achieve regulatory approval. We expect that coverage and reimbursement by government and private payors will be essential for most patients to be able to afford these treatments. Accordingly, sales of any such product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of any product candidates we may develop will be paid by government authorities, private health plans, and other third-party payors. Payors may not be willing to pay high prices for a single administration. Coverage and reimbursement by a third-party payor may depend upon several factors, including the third-party payor's determination that use of a product is:

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

Obtaining coverage and reimbursement for a product from third-party payors is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical, and cost-effectiveness data. There is significant uncertainty related to third-party coverage and reimbursement of newly approved products. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize any product candidates we may develop. Even if coverage is provided, the approved reimbursement amount may not be adequate to realize a sufficient return on our investment.

Moreover, the downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new product candidates such as ours. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell any product candidates we may develop will be harmed.

***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 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 focus our research and product development on treatments for rare genetically defined diseases. Many of our product candidates we may develop are expected to target a single mutation; as a result, the relevant patient population may therefore 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 develop could cure a target disease, we may not receive recurring revenues from patients and may deplete the patient population prevalence through curative therapy.

***If we are unable to successfully identify patients who are likely to benefit from therapy with any product candidates we develop, or experience significant delays in doing so, we may not realize the full commercial potential of any medicines we may develop.***

Our success may depend, in part, on our ability to identify patients who are likely to benefit from therapy with any medicines we may develop, which requires those potential patients to have their DNA analyzed for the presence or absence of a particular sequence. If we, or any third parties that we engage to assist us, are unable to successfully identify such patients, or experience delays in doing so, then:

- our ability to develop any product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials; and
- we may not realize the full commercial potential of any product candidates we develop that receive marketing approval if, among other reasons, we are unable to appropriately select patients who are likely to benefit from therapy with our medicines.

Any product candidates we develop may require use of a companion diagnostic to identify patients who are likely to benefit from therapy. If safe and effective use of any of our product candidates we may develop depends on a companion diagnostic, we may not receive marketing approval, or marketing approval may be delayed, if we are unable to or are delayed in developing, identifying, or obtaining regulatory approval or clearance for the companion diagnostic product for use with our product candidate. Identifying a manufacturer of the companion diagnostic and entering into an agreement with the manufacturer could also delay the development of our product candidates.

As a result of these factors, we may be unable to successfully develop and realize the commercial potential of any product candidates we may identify and develop, and our business, financial condition, results of operations, and prospects would be materially adversely affected.

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

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

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

Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage when we begin clinical trials and if we successfully commercialize any medicine. 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 we or any CMOs 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 CMOs 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 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 our current or past facilities and 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.

***Genetic medicines are novel, and any product candidates we develop may be complex and difficult to manufacture. We could experience delays in satisfying regulatory authorities or production problems that result in delays in our development or commercialization programs, limit the supply of our product candidates we may develop, or otherwise harm our business.***

Any product candidates we may develop will likely require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as the product candidates we intend to develop generally cannot be fully characterized. As a result, assays of the finished product candidate may not be sufficient to ensure that the product candidate will perform in the intended manner. 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 potential IND filings. If we successfully develop product candidates, we may encounter problems achieving adequate quantities and quality of clinical-grade materials that meet FDA, EMA or other comparable applicable foreign standards or specifications with consistent and acceptable production yields and costs. For example, the current approach of manufacturing AAV vectors may fall short of supplying required number of doses needed for advanced stages of preclinical studies or clinical trials, and the FDA may ask us to demonstrate that we have the appropriate manufacturing processes in place to support the higher-dose group in our future preclinical studies or clinical trials. In addition, our product candidates we may develop will require complicated delivery modalities, such as electroporation, LNPs, or viral vectors, each of which will introduce additional complexities in the manufacturing process.

In addition, the FDA, the EMA, and other regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, 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 clinical trials or product launches, which could be costly to us and otherwise harm our business, financial condition, results of operations, and prospects.

Furthermore, we intend to use novel split intein technology for any AAV gene therapy that allows us to deliver the base editor and guide RNA construct by co-infection with two viruses, where each virus contains one half of the editor. The scientific evidence to support the feasibility of developing product candidates based on this technology is both preliminary and limited.

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

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

Any problems in our manufacturing process or the facilities with which we contract could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs. Problems in third-party manufacturing process or facilities also could restrict our ability to ensure sufficient clinical material for any clinical trials we may be conducting or are planning to conduct and meet market demand for any product candidates we develop and commercialize.

## Risks related to our relationships with third parties

***We expect to rely on third parties to manufacture components of our product candidates we may develop, conduct our clinical trials and some aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research, or testing.***

We expect to rely on third parties, such as CMOs, CROs, clinical data management organizations, medical institutions, and clinical investigators, to manufacture components of our product candidates we may develop and to conduct our clinical trials. We currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical testing. For example, we rely on a third party to conduct electroporation; we rely on a third party to supply LNPs; and we rely on third parties to manufacture viral vectors. Any of these third parties may terminate their engagements with us at any time under certain criteria. If we need to enter into alternative arrangements, it may delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA, EMA and other regulatory authorities require us to comply with standards, commonly referred to as Good Clinical Practices, for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial participants are protected. In the United States, we also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity, and civil and criminal sanctions.

Although we intend to design the clinical trials for our product candidates, CROs 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 CROs 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 our product candidates 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 CROs 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.

***We contract with third parties for the manufacture of materials for our research programs, preclinical studies and clinical trial and expect to continue to do so for at least a portion of the manufacturing process for our research programs, preclinical studies, clinical trials and for commercialization of any product candidates that we may develop. This reliance on third parties increases the risk that we will not have sufficient quantities of such materials, product candidates, or any medicines that we may develop and commercialize, or that such supply will not be available to us at an acceptable cost, which could delay, prevent, or impair our development or commercialization efforts.***

We do not have any manufacturing facilities at the present time. We currently rely on third-party manufacturers for the manufacture of our materials for preclinical studies and clinical trial, and may continue to do so for at least a portion of the manufacturing process for our research programs, preclinical studies, clinical testing and for commercial supply of any product candidates that we may develop and for which we or our collaborators obtain marketing approval. We do not have a long-term supply agreement with any of the third-party manufacturers, and we purchase our required supply on an order-by-order basis.

While we announced that we are building a manufacturing facility designed to support manufacturing for our *ex vivo* cell therapy programs in hematology and oncology and *in vivo* non-viral delivery programs for liver diseases in Research Triangle Park, North Carolina, this facility is not yet operational and we cannot be certain that we will be able to build out our internal manufacturing capacity, or on the timeliness we expect.



We may be unable to establish long-term supply agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish long-term supply agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the possible breach of the manufacturing agreement by the third party;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- reliance on the third party for regulatory compliance, quality assurance, safety, and pharmacovigilance and related reporting; and
- the possible inability of third-party suppliers to supply and/or transport materials, components and products to us in a timely manner as a result of disruptions to the global supply chain in connection with the COVID-19 pandemic or other factors, or as a result of supply shortages in connection with large-scale production of COVID-19 vaccines.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocations, seizures or recalls of product candidates or medicines, operating restrictions, and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business, financial condition, results of operations, and prospects.

Any medicines that we develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing drug components and drug product necessary for gene editing. In addition, multiple third parties have contracted with commercial manufacturers to manufacture materials required for large-scale production of COVID-19 vaccines, including mRNA. If supply of mRNA is limited, we may not be able to obtain mRNA for use in our preclinical studies and clinical trials, which may result in research and development delays.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply of all drug components and drug products necessary for our gene editing product candidates. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture any product candidates we may develop, we may incur added costs and delays in identifying and qualifying any such replacement.

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

***As our drug development pipeline increases and matures, the increased demand for clinical supplies from our facilities and third parties may impact our ability to operate. We will require increased capacity across our entire supply chain. Furthermore, we rely on many service providers, including those that provide manufacturing or testing services, all of whom have inherent risks in their operations that may adversely impact our operations.***

Completion of our clinical trials and commercialization of our product candidates require access to, or development of, facilities to manufacture our product candidates at sufficient yields and, if approved, at commercial-scale. We have limited experience manufacturing any of our product candidates in the volumes that are necessary to support clinical trials or and no experience manufacturing at volumes that are necessary to support commercial sales. Efforts to establish these capabilities may not meet initial expectations as to scheduling, scale-up, reproducibility, yield, purity, cost, potency or quality. In addition, other companies, many with substantial resources, compete with us for access to the materials needed to manufacture our product candidates.

We currently utilize, and expect to continue to utilize, third parties to, among other things, manufacture raw materials, components, parts, and consumables, and to perform quality testing. If the field of base editing and other genetic medicines continues to expand, we may encounter increasing competition for these materials and services. Demand for third-party manufacturing or testing facilities may grow at a faster rate than their existing capacity, which could disrupt our ability to find and retain third-party manufacturers capable of producing sufficient quantities of such raw materials, components, parts, and consumables required to manufacture our product candidates. The use of service providers and suppliers could expose us to risks, including, but not limited to:

- termination or non-renewal of supply and service agreements with third parties in a manner or at a time that is costly or damaging to us;
- disruptions to the operations of these suppliers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the supplier or service provider; and
- inspections of third-party facilities by regulatory authorities that could have a negative outcome and result in delays to or termination of their ability to supply our requirements.

Our reliance on third-party manufacturers may adversely affect our operations or result in unforeseen delays or other problems beyond our control. Because of contractual restraints and the limited number of third-party manufacturers with the expertise, required regulatory approvals and facilities to manufacture our product candidates on a clinical and, if approved, a commercial scale, replacement of a manufacturer may be expensive and time-consuming and may cause interruptions in the production of our product candidates. A third-party manufacturer may also encounter difficulties in production. These problems may include:

- difficulties with production costs, scale up and yields;
- availability of raw materials and supplies;
- quality control and assurance;
- shortages of qualified personnel;
- compliance with strictly enforced federal, state and foreign regulations that vary in each country where products might be sold; and
- lack of capital funding.

As a result, any delay or interruption could have a material adverse effect on our business, financial condition, or results of operations.

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

We have and may in the future seek third-party collaborators for the research, development, and commercialization of certain of the product candidates we develop. Under the agreements we have entered into and any agreements we may enter into in the future with any third parties, we have and 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 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 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 clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing.
- Collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our medicines or product candidates we 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 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 product candidates or that result in costly litigation or arbitration that diverts management attention and resources.
- We may lose certain valuable rights under circumstances identified in our collaborations, 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.
- 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. Furthermore, even if we receive such payments, they will likely result in payment obligations under license agreements with our licensors, which could be substantial. If we do not receive the funding we expect under these collaboration agreements, or if the funding is substantially offset by payment obligations to our licensors, 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 on Form 10-K 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 may develop 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 collaborators and strategic partners 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, or fail to devote sufficient resources to the development and commercialization of products. 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.

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

We may not be able to negotiate 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, if approved, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or, if approved, commercialization activities at our own expense. If we elect to increase our expenditures to fund development or, if approved, commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to develop product candidates or bring them to market and generate product revenue.

#### **Risks related to our intellectual property**

***If we are unable to obtain and maintain patent and other intellectual property protection for any product candidates we develop and for our platform technologies, or if the scope of the patent and 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 commercialize any product candidates we may develop, and our platform technologies may be adversely affected.***

Our commercial success will depend in large part on our ability to obtain and maintain patent, trademark, trade secret and other intellectual property protection of our base editing platform technology, product candidates and other technology, including delivery platform technology methods used to manufacture them and methods of treatment, as well as successfully defending our patent and other intellectual property rights against third-party challenges. It is difficult and costly to protect our base editing platform technology and protect candidates, and we may not be able to ensure their protection. Our ability to stop unauthorized third parties from making, using, selling, offering to sell, importing or otherwise commercializing our product candidates we may develop is dependent upon the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities.

We seek to protect our proprietary position by in-licensing intellectual property relating to our platform technology and filing patent applications in the United States and abroad related to our base editing platform technology, delivery platform technology and product candidates that are important to our business. If we or our licensors are unable to obtain or maintain patent protection with respect to our base editing platform technology, delivery platform technology and product candidates we may develop, or if the scope of the patent protection secured is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours and our ability to commercialize any product candidates we may develop may be adversely affected.

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, we may not pursue or obtain patent protection in all relevant markets. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in our owned or any licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. The field of gene editing, especially in the area of base editing technology, has been the subject of extensive patenting activity and litigation. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain, and we may become involved in complex and costly litigation. Our pending and future patent applications may not result in patents being issued which protect our base editing platform technology, delivery platform technology and product candidates we may develop, or which effectively prevent others from commercializing competitive technologies and product candidates.

No consistent policy regarding the scope of claims allowable in the field of gene editing, including base editing technology, has emerged in the United States. The scope of patent protection outside of the United States is also uncertain. Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions, obtain, maintain, enforce and defend our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our owned and licensed patent rights. With respect to both in-licensed and owned intellectual property, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will be valid and enforceable and provide sufficient protection from competitors.

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we license or own currently or in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. Any patents that we own, or in-license, may be challenged, narrowed, circumvented, or invalidated by third parties. Consequently, we do not know whether any of our platform advances and product candidates we may develop will be protectable or remain protected by valid and enforceable patents. 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.

In addition, given the amount of time required for the development, testing, and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Moreover, some of our owned and in-licensed patents and patent applications are, and may in the future be, co-owned by us with third parties. For example, a patent application directed to our potential HBG1 and HBG2 product candidates is co-owned by us, the President and Fellows of Harvard College, or Harvard, and Broad Institute. At present, we do not have a license to the ownership interest of Harvard or Broad Institute. If we are unable to obtain an exclusive license to such third-party co-owners' interest in such patents or patent applications, such 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. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. 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 our base editing platform technology and product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.***

We depend on intellectual property licensed from third parties, and our licensors may not always act in our best interest. If we fail to comply with our obligations under our intellectual property licenses, if the licenses are terminated, or if disputes regarding these licenses arise, we could lose significant rights that are important to our business.

We have licensed and are dependent on certain patent rights and proprietary technology from third parties that are important or necessary to the development of our base editing technology and product candidates. For example, we are a party to license agreements with Broad Institute, Editas, Harvard, and Bio Palette, and others, pursuant to which we in-license key patents and patent applications for our base editing platform technology and product candidates (the Broad License Agreement, the Editas License Agreement, the Harvard License Agreement and the Bio Palette License Agreement, respectively). These license agreements impose various diligence, milestone payment, royalty, insurance, and other obligations on us. If we fail to comply with these obligations, our licensors may have the right to terminate our license, in which event we would not be able to develop or market our base editing platform or any other technology or product candidates covered by the intellectual property licensed under these agreements. For example, under the Harvard License Agreement, we are required to initiate a discovery program in accordance with the development plan and development milestones for the development of a licensed product covered by certain sub-categories of licensed patents. If we fail to initiate such a discovery program, our rights with respect to the sub-category of licensed patents will terminate.

These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our base editing platform technology and product candidates in the future. Some licenses granted to us are expressly subject to certain preexisting rights held by the licensor or certain third parties. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in certain territories or fields. For example, certain licensed patents developed by employees of the Howard Hughes Medical Institute, or HHMI, and subsequently assigned to Harvard and licensed to us under the Harvard License Agreement remain subject to a non-exclusive license between Harvard and HHMI. The Editas License Agreement provides that our field of use excludes the diagnosis, treatment, and prevention of human cancers through certain engineered T-cells, which are licensed to Juno Therapeutics, Inc. (a subsidiary of Bristol-Myers Squibb Company). If we determine that rights to such excluded field are necessary to commercialize our product candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to continue developing, manufacturing or marketing our product candidates. We may not be able to obtain such a license on an exclusive basis, on commercially reasonable terms, or at all, which could prevent us from commercializing our product candidates or allow our competitors or others the chance to access technology that is important to our business.

Under the Broad License Agreement, rights granted to us include certain patent applications directed to Cas12b or Cas13 that are limited to the United States. The co-owners of these patent applications include Broad Institute, Harvard, MIT, the State University of New Jersey, or Rutgers, Skolkovo Institute of Science and Technology, or Skoltech, and the NIH. At present, we do not have a license to the ownership interest of Rutgers, Skoltech, or the NIH. If we are unable to obtain an exclusive license to Rutgers, Skoltech, and the NIH's interest in such patent applications, Rutgers, Skoltech, and the NIH may be able to license its rights to other third parties, including our competitors, and such third parties could market competing products and technology. In addition, we may need the cooperation of Rutgers, Skoltech, or the NIH in order to enforce patents issuing from these patent applications against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

In addition, pursuant to our license agreement with Broad Institute and our license agreement with Harvard, under certain specific circumstances (in each case), Broad Institute or Harvard (as applicable) may grant a license to the patents that are the subject of such license agreement to a third party in the same field as such patents are licensed to us. Such third party may then have full rights that are the subject of the Broad License Agreement or the Harvard License Agreement (as applicable), which could impact our competitive position and enable a third party to commercialize products similar to our potential future product candidates and technology. Any grant of rights to a third party in this scenario would narrow the scope of our exclusive rights to the patents and patent applications we have in-licensed from Broad Institute and/or Harvard, as applicable.

We do not have complete control in the preparation, filing, prosecution, maintenance, enforcement, and defense of patents and patent applications covering the technology that we license from third parties. For example, pursuant to each of our intellectual property licenses with Broad Institute, Harvard, Editas and Bio Palette, 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' 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, or may not be conducted in accordance with our best interests. 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 prosecute, maintain, enforce, and defend such patents, 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 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 from making, using, and selling competing products.

Our licensors may have relied on third-party consultants or collaborators or on funds from third parties such that our licensors are not the sole and exclusive owners of the patents we in-licensed. If other third parties have ownership rights to our in-licensed patents, the license granted to us in jurisdictions where the consent of a co-owner is necessary to grant such a license may not be valid and such co-owners may be able to license such patents to our competitors, and our competitors could market competing products and technology. In addition, our rights to our in-licensed patents and patent applications are dependent, in part, on inter-institutional or other operating agreements between the joint owners of such in-licensed patents and patent applications. If one or more of such joint owners breaches such inter-institutional or operating agreements, our rights to such in-licensed patents and patent applications may be adversely affected. Any of these events could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Furthermore, inventions contained within some of our in-licensed patents and patent applications were made using U.S. government funding. We rely on our licensors to ensure compliance with applicable obligations arising from such funding, such as timely reporting, an obligation associated with our in-licensed patents and patent applications. The failure of our licensors to meet their obligations may lead to a loss of rights or the unenforceability of relevant patents. For example, the U.S. government could have certain rights in such in-licensed patents, 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 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 also 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 product candidates embodying such inventions in the United States. Any of the foregoing could harm our business, financial condition, results of operations, and prospects significantly.

In the event any of our third-party licensors determine that, in spite of our efforts, we have materially breached a license agreement or have failed to meet certain obligations thereunder, it may elect to terminate the applicable license agreement or, in some cases, one or more licenses under the applicable license agreement and such termination would result in us no longer having the ability to develop and commercialize product candidates and technology covered by that license agreement or license. In the event of such termination of a third-party in-license, or if the underlying patents under a third-party in-license fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. Any of these events could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

***Our owned and in-licensed patents and patent applications may not provide sufficient protection of our platform technologies, our product candidates and our future product candidates or result in any competitive advantage.***

We have in-licensed a number of issued U.S. patents and patent applications that cover base editing and gene targeting technologies, as well as our delivery platform technology. We have applied for provisional patent applications or Patent Cooperation Treaty, or PCT, applications intended to specifically cover our base editing platform technology and uses with respect to treatment of particular diseases and conditions, and currently own two issued U.S. patents. We have applied for provisional patent applications or PCT applications intended to specifically cover our delivery platform technology but do not currently own any issued U.S. patents. Each U.S. provisional patent application is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of the filing date of the applicable provisional patent application. Any failure to file a non-provisional patent application within this timeline could cause us to lose the ability to obtain patent protection for the intentions disclosed in the associated provisional patent applications. We cannot be certain that any of these patent applications will issue as patents, and if they do, that such patents will cover or adequately protect our base editing platform technology, delivery platform technology or our product candidates, or that such patents will not be challenged, narrowed, circumvented, invalidated or held unenforceable. Any failure to obtain or maintain patent protection with respect to our base editing platform technology, delivery platform technology and product candidates could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Our owned patents and patent applications and our in-licensed patents and patent applications contain claims directed to compositions of matter on our base editing product candidates, as well as methods directed to the use of such product candidates for gene therapy treatment. Method-of-use patents do not prevent a competitor or other third party from developing or marketing an identical product for an indication that is outside the scope of the patented method. Moreover, with respect to method-of-use patents, even if competitors or other third parties do not actively promote their product for our targeted indications or uses for which we may obtain patents, providers may recommend that patients use these products off-label, or patients may do so themselves.

The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. The patent applications that we own, or in-license, may fail to result in issued patents with claims that cover our product candidates or uses thereof in the United States or in other foreign countries. For example, while our patent applications are pending, we may be subject to a third-party pre-issuance submission of prior art to the United States Patent and Trademark Office, or USPTO, or become involved in interference or derivation proceedings, or equivalent proceedings in foreign jurisdictions. Even if patents do successfully issue, third parties may challenge their inventorship, validity, enforceability or scope, including through opposition, revocation, reexamination, post-grant and *inter partes* review proceedings. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our owned or in-licensed patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize 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 our or our licensor's priority of invention or other features of patentability with respect to our owned or in-licensed patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity, or in patent claims being narrowed, invalidated, or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing around our claims. If the breadth or strength of protection provided by the patents and patent applications we own or the patents and patent applications we in-license with respect to our base editing platform technology, delivery platform technology and product candidates is threatened, it could dissuade companies from collaborating with us to develop, and threaten our ability to commercialize, our product candidates. Further, if we encounter delays in development, testing, and regulatory review of new product candidates, the period of time during which we could market our product candidates under patent protection would be reduced.

Given that patent applications in the United States and other countries are confidential for a period of time after filing, at any moment in time, we cannot be certain that we or our licensors were in the past or will be in the future the first to file any patent application related to our base editing technology, delivery platform technology or product candidates. In addition, some patent applications in the United States may be maintained in secrecy until the patents are issued. As a result, there may be prior art of which we or our licensors are not aware that may affect the validity or enforceability of a patent claim, and we or our licensors may be subject to priority disputes. For our in-licensed patent portfolios, we rely on our licensors to determine inventorship, and obtain and file inventor assignments of priority applications before their conversion as PCT applications. A failure to do so in a timely fashion may give rise to a challenge to entitlement of priority for foreign applications nationalized from such PCT applications. For example, the European Patent Office, or the EPO, Opposition Division, or the EPO Opposition Division, has revoked our optioned Broad Institute patent European Patent No. EP2771468 following a third-party challenge to its priority rights. The patent was revoked due to loss of priority. We or our licensors are subject to and may in the future become a party to proceedings or priority disputes in Europe or other foreign jurisdictions. The loss of priority for, or the loss of, these European patents could have a material adverse effect on the conduct of our business.

We may be required to disclaim part or all of the term of certain patents or patent applications. There may be prior art of which we are not aware that may affect the validity or enforceability of a patent claim. There also may be prior art of which we or our licensors are aware, but which we or our licensors do not believe affects the validity or enforceability of a claim, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. No assurance can be given that, if challenged, our patents would be declared by a court, patent office or other governmental authority to be valid or enforceable or that even if found valid and enforceable, a competitor's technology or product would be found by a court to infringe our patents. We may analyze patents or patent applications of our competitors that we believe are relevant to our activities, and consider that we are free to operate in relation to our product candidates, but our competitors may achieve issued claims, including in patents we consider to be unrelated, that block our efforts or potentially result in our product candidates or our activities infringing such claims. It is possible that our competitors may have filed, and may in the future file, patent applications covering our products or technology similar to ours. Those patent applications may have priority over our owned patent applications and in-licensed patent applications or patents, which could require us to obtain rights to issued patents covering such technologies. The possibility also exists that others will develop products that have the same effect as our product candidates on an independent basis that do not infringe our patents or other intellectual property rights, or will design around the claims of our patent applications or our in-licensed patents or patent applications that cover our product candidates.



Likewise, our currently owned patents and patent applications, if issued as patents, and in-licensed patents and patent applications, if issued as patents, directed to our proprietary base editing technologies and our product candidates are expected to expire from 2034 through 2043, without taking into account any possible patent term adjustments or extensions. Our owned or in-licensed patents may expire before, or soon after, our first product candidate achieves marketing approval in the United States or foreign jurisdictions. Additionally, no assurance can be given that the USPTO or relevant foreign patent offices will grant any of the pending patent applications we own or in-license currently or in the future. Upon the expiration of our current in-licensed patents, we may lose the right to exclude others from practicing these inventions. The expiration of these patents could also have a similar material adverse effect on our business, financial condition, results of operations and prospects.

***Our owned patents and patent applications and in-licensed patents and patent applications and other intellectual property may be subject to priority disputes or to inventorship disputes and similar proceedings. If we or our licensors are unsuccessful in any of these proceedings, we may be required to obtain licenses from third parties, which may not be available on commercially reasonable terms or at all, or to cease the development, manufacture, and commercialization of one or more of the product candidates we may develop, which could have a material adverse impact on our business.***

Although we have an option to exclusively license certain patents and patent applications directed to Cas9 and Cas12a from Editas, who in turn has licensed such patents from various academic institutions including Broad Institute, we do not currently have a license to such patents and patent applications. Certain of the U.S. patents and one U.S. patent application to which we hold an option are co-owned by Broad Institute and MIT, and in some cases co-owned by Broad Institute, MIT, and Harvard, which we refer to together as the Boston Licensing Parties, and were involved in U.S. interference No. 106,048 with one U.S. patent application co-owned by the University of California, the University of Vienna, and Emmanuelle Charpentier, which we refer to together as the University of California. On September 10, 2018, the Court of Appeals for the Federal Circuit, or the CAFC, affirmed the Patent Trial and Appeal Board of the USPTO's, or PTAB's, holding that there was no interference-in-fact. An interference is a proceeding within the USPTO to determine priority of invention of the subject matter of patent claims filed by different parties.

On June 24, 2019, the PTAB declared an interference (U.S. Interference No. 106,115) between ten U.S. patent applications ((U.S. Serial Nos. 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; and 16/136,175) that are co-owned by the University of California, and 13 U.S. patents and one U.S. patent application (U.S. Patent Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; and 9,840,713, and U.S. Serial No. 14/704,551)) that are co-owned by the Boston Licensing Parties, which we have an option to under the Editas License Agreement. In the declared interference, the University of California has been designated as the junior party and the Boston Licensing Parties have been designated as the senior party.

As a result of the declaration of interference, an adversarial proceeding in the USPTO before the PTAB has been initiated, which is declared to ultimately determine priority, specifically and which party was first to invent the claimed subject matter. Following oral arguments on the parties' motions in May 2020, the PTAB issued a decision in September 2020, which included, in part, denying the Boston Licensing Parties motion that the University of California should be estopped in the current proceeding by the PTAB's decision in the prior interference proceeding between the parties (No. 106,048), finding that the Boston Licensing Parties remain the senior party in the proceeding, and holding that the interference will proceed to the second, priority phase. An interference is typically divided into two phases. The first phase is referred to as the motions or preliminary motions phase while the second is referred to as the priority phase. In the first phase, each party may raise issues including but not limited to those relating to the patentability of a party's claims based on prior art, written description, and enablement. A party also may seek an earlier priority benefit or may challenge whether the declaration of interference was proper in the first place. Priority, or a determination of who first invented the commonly claimed invention, is determined in the second phase of an interference. We cannot predict with any certainty how long the priority phase will actually take, and it may take approximately a year or longer before a decision is made by the PTAB. On February 4, 2022 an oral hearing was held in the priority phase of U.S. Interference No. 106,048. Although the hearing typically precedes a decision by the PTAB, we cannot predict with any certainty when a decision will be made. The ten University of California patent applications and the 13 U.S. patents and one U.S. patent application co-owned by the Boston Licensing Parties involved in U.S. Interference No. 106,115 generally relate to CRISPR/Cas9 systems or eukaryotic cells comprising CRISPR/Cas9 systems having fused or covalently linked RNA and the use thereof in eukaryotic cells. There can be no assurance that the U.S. interference will be resolved in favor of the Boston Licensing Parties. If the U.S. interference resolves in favor of University of California, or if the Boston Licensing Parties' patents and patent application are narrowed, invalidated, or held unenforceable, we may lose the ability to license the optioned patents and patent application and our ability to commercialize our product candidates may be adversely affected if we cannot obtain a license to relevant third party patents that cover our product candidates. 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 nonexclusive, 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. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our base editing platform technology or product candidates or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

We or our licensors may be subject to similar interferences in the future with the same risks as described above. For example, on December 14, 2020, the PTAB declared an interference (U.S. Interference No. 106,126) between 14 U.S. patents and two U.S. patent applications (U.S. Patent Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,889,418; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; and 9,840,713, and U.S. Serial Nos. 14/704,551 and 15/330,876) that are co-owned by the Boston Licensing Parties, which we have an option to under the Editas License Agreement, and one U.S. patent application (U.S. Serial Nos. 14/685,510) that is owned by Toolgen, Inc. or Toolgen. In the declared interference, the Boston Licensing Parties have been designated as the junior party and Toolgen has been designated as the senior party. In March 2021, the PTAB issued an order on preliminary motions, granting, in part, and denying, in part, certain motions proposed by the Boston Licensing Parties and Toolgen. Although we cannot predict with any certainty how long the preliminary motions phase will actually take, it may take approximately a year or longer before a decision on the motions is made by the PTAB. The 14 U.S. patents and two U.S. patent applications co-owned by the Boston Licensing Parties involved in U.S. Interference No. 106,126 generally relate to CRISPR/Cas9 systems or eukaryotic cells comprising CRISPR/Cas9 systems having fused or covalently linked RNA and the use thereof in eukaryotic cells.

On June 21, 2021, the PTAB declared an interference (U.S. Interference No. 106,133) between the same 14 U.S. patents and two U.S. patent applications (U.S. Patent Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,889,418; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; and 9,840,713, and U.S. Serial Nos. 14/704,551 and 15/330,876, co-owned by the Boston Licensing Parties) as named in the interference with Toolgen, and one U.S. patent application (U.S. Serial Nos. 15/456,204) that is owned by Sigma-Aldrich Co., LLC, or Sigma-Aldrich. In the declared interference, the Boston Licensing Parties have been designated as the junior party and Sigma-Aldrich has been designated as the senior party. In September 2021, the PTAB issued an order on preliminary motions, granting, deferring, dismissing, or denying, certain motions proposed by the Boston Licensing Parties and Sigma-Aldrich.

We or our licensors may also be subject to claims that former employees, collaborators, or other third parties have an interest in our owned patents or patent applications or in-licensed patents or patent applications or other intellectual property as an inventor or co-inventor. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors. In addition, we may need the cooperation of any such co-owners to enforce any patents that issue from such patent applications against third parties, and such cooperation may not be provided to us.

If we or our licensors are unsuccessful in any interference proceedings or other priority, validity (including any patent oppositions), or inventorship disputes to which we or they are subject, we may lose valuable intellectual property rights through the loss of one or more of our owned, licensed, or optioned patents, or such patent claims may be narrowed, invalidated, or held unenforceable, or through loss of exclusive ownership of or the exclusive right to use our owned or in-licensed patents. In the event of loss of patent rights as a result of any of these disputes, we may be required to obtain and maintain licenses from third parties, including parties involved in any such interference proceedings or other priority or inventorship disputes. Such licenses may not be available on commercially reasonable terms or at all, or may be non-exclusive. If we are unable to obtain and maintain such licenses, we may need to cease the development, manufacture, and commercialization of one or more of the product candidates we may develop. The loss of exclusivity or the narrowing of our patent claims could limit our ability to stop others from using or commercializing similar or identical technology and product candidates. Even if we or our licensors are successful in an interference proceeding or other similar priority or inventorship disputes, it could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could result in a material adverse effect on our business, financial condition, results of operations, or prospects.

***We have limited foreign intellectual property rights and may not be able to protect our intellectual property and proprietary rights throughout the world.***

We have limited intellectual property rights outside the United States. Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of foreign countries do not protect intellectual property rights to the same extent as federal and state laws of the United States. In addition, our intellectual property license agreements may not always include worldwide rights. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but where enforcement is not as strong as that in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

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

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

***If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.***

We have entered into license agreements with third parties and may need to obtain additional licenses from our existing licensors and others to advance our research or allow commercialization of product candidates we may develop. It is possible that we may be unable to obtain any additional licenses at a reasonable cost or on reasonable terms, if at all. In either event, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business, financial condition, results of operations, and prospects significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current technology, including base editing technology, delivery platform technology, manufacturing methods, product candidates, or future methods or products resulting in either an injunction prohibiting our manufacture or future sales, or, with respect to our future sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties, which could be significant.

In each of our license agreements, we are generally responsible for bringing any actions against any third party for infringing on the patents we have licensed. Certain of our license agreements, also require us to meet development thresholds to maintain the license, including establishing a set timeline for developing and commercializing products. In spite of our efforts, our licensors might conclude that we have materially breached our obligations under such license agreements and might therefore terminate the license agreements, thereby removing or limiting our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors or other third parties would have the freedom to seek regulatory approval of, and to market, products identical to ours and we may be required to cease our development and commercialization of or base editing platform technology, delivery platform technology or product candidates. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and growth 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;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights to third parties under our collaborative development relationships;
- our diligence obligations under the license agreement with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we currently license intellectual property or technology from third parties are 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 broaden what we believe to be the scope of the licensor's rights to our intellectual property and technology, or increase what we believe to be our financial or other obligations under the relevant agreement, any of which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates. As a result, any termination of or disputes over our intellectual property licenses could result in the loss of our ability to develop and commercialize our base editing platform, delivery platform, or other product candidates or we could lose other significant rights, any of which could have a material adverse effect on our business, financial conditions, results of operations, and prospects. It is also possible that a third party could be granted limited licenses to some of the same technology, in certain circumstances.

***We may not be successful in acquiring or in-licensing necessary rights to key technologies or any product candidates we may develop.***

We currently have rights to intellectual property, through licenses from third parties, to identify and develop product candidates, and we expect to seek to expand our product candidate pipeline in part by in-licensing the rights to key technologies. The future growth of our business will depend in part on our ability to in-license or otherwise acquire the rights to additional product candidates and technologies. Although we have succeeded in licensing technologies from third party licensees including Harvard, Broad Institute, Editas, and Bio Palette in the past, we cannot assure you that we will be able to in-license or acquire the rights to any product candidates or technologies from third parties on acceptable terms or at all.

For example, our agreements with certain of our third-party licensors provide that our field of use excludes particular fields, for example, the diagnosis, treatment, and prevention of human cancers through certain engineered T-cells, which are licensed exclusively or non-exclusively to a third-party licensee. If we determine that rights to such fields are necessary to commercialize our drug candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to continue developing, manufacturing or marketing our drug candidates. We may not be able to obtain such a license on an exclusive basis, on commercially reasonable terms, or at all, which could prevent us from commercializing our drug candidates or allow our competitors or others the chance to access technology that is important to our business.

Furthermore, there has been extensive patenting activity in the fields of gene editing and delivery technologies, and pharmaceutical companies, biotechnology companies, and academic institutions are competing with us or are expected to compete with us in the fields of gene editing and delivery technologies and filing patent applications potentially relevant to our business and we are aware of certain third-party patent applications that, if issued, may allow the third party to circumvent our patent rights. For example, we are aware of several third-party patents, and patent applications, that if issued, may be construed to cover our base editing technology, delivery technology and product candidates. In order to market our product candidates, we may find it necessary or prudent to obtain licenses from such third-party intellectual property holders. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for product candidates we may develop and base editing and delivery technologies. We may also require licenses from third parties for additional non-base editing technologies, including additional delivery methods that we are evaluating for use with product candidates we are developing and may develop in the future. In addition, some of our owned patents and patent applications and in-licensed patents and patent applications are co-owned with third parties. With respect to any patents co-owned with third parties, we may require licenses to such co-owners' interest to such patents. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such 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. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us.

Additionally, we may collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Even if we hold such an option, we may be unable to negotiate a license from the institution 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 others, potentially blocking our ability to pursue our program.

In addition, the licensing or acquisition of third-party intellectual property rights is a highly competitive area, and a number of more established companies are also pursuing strategies to license or acquire third party intellectual property rights that we may consider attractive 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 or at all. If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

***The intellectual property landscape around gene editing technology, including base editing and delivery technology, is highly dynamic, and 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 may prevent, delay or otherwise interfere with our product discovery and development efforts.***

The field of gene editing, especially in the area of base editing technology, is still in its infancy, and no such product candidates have reached the market. Due to the intense research and development that is taking place by several companies, including us and our competitors, in this field and in the field of delivery technology, the intellectual property landscape is evolving and in flux, and it may remain uncertain for the coming years. There may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third party, intellectual property and proprietary rights in the future.

Our commercial success depends upon our ability and the ability of our collaborators and licensors to develop, manufacture, market, and sell any product candidates that we may develop and use our proprietary technologies without infringing, misappropriating, or otherwise violating the intellectual property and proprietary rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights as well as administrative proceedings for challenging patents, including interference, derivation, *inter partes* review, post grant review, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. We may be subject to and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our base editing platform technology, delivery platform technology and any product candidates we may develop, including interference proceedings, post-grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in foreign jurisdictions such as oppositions before the EPO. Numerous U.S. and foreign issued patents and pending patent applications that are owned by third parties exist in the fields in which we are developing our product candidates and they may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit.

As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our base editing platform technology, delivery platform technology and product candidates may give rise to claims of infringement of the patent rights of others. Moreover, it is not always clear to industry participants, including us, which patents cover various types of therapies, products or their methods of use or manufacture. We are aware of certain third-party patents and patent applications that, if issued, may be construed to cover our base editing technology, delivery technology and product candidates. There may also be third-party patents of which we are currently unaware with claims to technologies, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents.

Numerous third-party U.S. and foreign issued patents and pending patent applications exist in the fields in which we are developing product candidates. Our product candidates make use of CRISPR-based technology, which is a field that is highly active for patent filings. The extensive patent filings related to CRISPR and Cas make it difficult for us to assess the full extent of relevant patents and pending applications that may cover our base editing platform technology and product candidates and their use or manufacture. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our base editing platform technology and product candidates. For example, we are aware of a patent portfolio that is co-owned by the University of California, University of Vienna and Emmanuelle Charpentier, or the University of California Portfolio, which contains multiple patents and pending applications directed to gene editing. The University of California portfolio includes, for example, U.S. Patent Nos. 10,266,850; 10,227,611; 10,000,772; 10,113,167; 10,301,651; 10,308,961; 10,337,029; 10,351,878; 10,407,697; 10,358,659; 10,358,658; 10,385,360; 10,400,253; 10,421,980; 10,415,061; 10,428,352; 10,443,076; 10,487,341; 10,513,712; 10,519,467; 10,526,619; 10,533,190; 10,550,407; 10,563,227; 10,570,419; 10,577,631; 10,597,680; 10,612,045; 10,626,419; 10,640,791; 10,669,560; 10,676,759; 10,752,920; 10,774,344; 10,793,878; 10,900,054; 10,982,230; 10,982,231; 10,988,780; 10,988,782; 11,001,863; 11,008,589; 11,008,590; 11,028,412; 11,186,849; 11,242,543, which are expected to expire around March 2033, excluding any additional term for patent term adjustment, or PTA, or patent term extension, or PTE, and any disclaimed term for terminal disclaimers. The University of California portfolio also includes numerous additional pending patent applications. If these patent applications issue as patents, they are expected to expire around March 2033, excluding any PTA, PTE, and any disclaimed term for terminal disclaimers. As discussed above, certain applications in the University of California Portfolio are currently subject to U.S. Interference No. 106,115 with certain U.S. patents and one U.S. patent application that are co-owned by the Boston Licensing Parties to which we have an option under the Editas License Agreement. Although we have an option to exclusively license certain patents and patent applications directed to Cas9 and Cas12a from Editas, who in turn has licensed such patents from various academic institutions including Broad Institute, we do not currently have a license to such patents and patent applications. Certain members of the University of California Portfolio are being opposed in Europe by multiple parties. For example, the EPO Opposition Division has initiated opposition proceedings against European Patent Nos. EP2,800,811 B1, and EP3,241,902 B1 and EP3,401,400 B1, which are estimated to expire in March 2033 (excluding any patent term adjustments or extensions). The opposition procedure before the EPO allows one or more third parties to challenge the validity of a granted European patent within nine months after grant date of the European patent. Opposition proceedings may involve issues including, but not limited to, priority, patentability of the claims involved, and procedural formalities related to the filing of the patent application. As a result of the opposition proceedings, the Opposition Division can revoke a patent, maintain the patent as granted, or maintain the patent in an amended form. Most of the claims of European patent EP 2,800,811 B1 were maintained without amendment by the Opposition Division, but this decision is being appealed. In April 2021, the claims of European patent EP3,241,902 B1 were revoked in their entirety, and that decision is not being appealed. In February 2022, the claims of European patent EP3,401,400 B1 were maintained in amended form by the Opposition Division, and it is uncertain if this decision will be appealed. If these patents are maintained by the Opposition Division with claims similar to those that are currently opposed, our ability to commercialize our product candidates may be adversely affected if we do not obtain a license to these patents. 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 nonexclusive, 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. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our base editing platform technology or product candidates or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

Numerous other patents and patent applications have been filed by other third parties directed to gene editing, guide nucleic acids, PAM sequence variants, split inteins, Cas12b or gene editing in the context of immune therapy or chimeric antigen receptors.

Because of the large number of patents issued and patent applications filed in our field, third parties may allege they have patent rights encompassing our product candidates, technologies or methods. Third parties may assert that we are employing their proprietary technology without authorization and may file patent infringement claims or lawsuit against us, and if we are found to infringe such third-party patents, we may be required to pay damages, cease commercialization of the infringing technology, or obtain a license from such third parties, which may not be available on commercially reasonable terms or at all.

Our ability to commercialize our product candidates in the United States and abroad may be adversely affected if we cannot obtain a license on commercially reasonable terms to relevant third-party patents that cover our product candidates, delivery platform technology or base editing platform technology. Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, enforceability, or priority. A court of competent jurisdiction could hold that these third-party patents are valid, enforceable, and infringed, which could materially and adversely affect our ability to commercialize any product candidates we may develop and any other 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 intellectual property rights, and we are unsuccessful in demonstrating that such patents are invalid or unenforceable, 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. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our base editing platform technology, delivery platform technology or product candidates or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business. We also 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 significant monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar material adverse effect on our business, financial condition, results of operations, and prospects.

Defense of third-party claims of infringement of misappropriation, or violation of intellectual property rights involves substantial litigation expense and would be a substantial diversion of management and employee time and resources from our business. Some third parties may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations or could otherwise have a material adverse effect on our business, financial condition, results of operations and prospects. There could also 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. Any of the foregoing events could have a material adverse effect on our business, financial condition, results of operations and prospects.

***We may become involved in lawsuits to protect or enforce our patents, future patents or the patents of our licensors, which could be expensive, time consuming, and unsuccessful and could result in a finding that such patents are unenforceable or invalid.***

Competitors may infringe our patents, future patents or the patents of our licensing partners, or we may be required to defend against claims of infringement. In addition, our patents, future patents or the patents of our licensing partners also are, and may in the future become, involved in inventorship, priority, validity or enforceability disputes. Countering or defending against such claims can be expensive and time consuming. In an infringement proceeding, a court may decide that a patent owned or in-licensed by us is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our owned and in-licensed patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly.

In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. These types of mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). These types of proceedings could result in revocation or amendment to our patents such that they no longer cover our product candidates. The outcome for any particular patent 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 we, our licensors, our patent counsel and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, or if we are otherwise unable to adequately protect our rights, we would lose at least part, and perhaps all, of the patent protection on our technology and/or product candidates. Defense of these types of claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business.

Conversely, we may choose to challenge the patentability of claims in a third party's U.S. patent by requesting that the USPTO review the patent claims in re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). We are currently challenging, and in the future may choose to challenge, third party patents in patent opposition proceedings in the EPO or another foreign patent office. Even if successful, the costs of these opposition proceedings could be substantial, and may consume our time or other resources. If we fail to obtain a favorable result at the USPTO, EPO or other patent office then we may be exposed to litigation by a third party alleging that the patent may be infringed by our product candidates, base editing platform technology, delivery platform technology or other or proprietary technologies.

For example, as discussed above, elements of the University of California patent portfolio are being opposed in Europe by multiple parties and we are participating in the opposition proceedings. The EPO Opposition Division, or the Opposition Division, has initiated opposition proceedings against European patents estimated to expire in March 2033 (excluding any patent term adjustments or extensions) and co-owned by the University of California. The opposition procedure before the EPO allows one or more third parties to challenge the validity of a granted European patent within nine months after grant date of the European patent. Opposition proceedings may involve issues including, but not limited to, priority, patentability of the claims involved, and procedural formalities related to the filing of the patent application. As a result of the opposition proceedings, the Opposition Division can revoke a patent, maintain the patent as granted, or maintain the patent in an amended form. It is uncertain when or in what manner the Opposition Division will act on the opposition proceedings of these European patents. If these patents are maintained by the Opposition Division with claims similar to those that are currently opposed, our ability to commercialize our product candidates may be adversely affected if we do not obtain a license to these patents. 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 nonexclusive, 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. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our base editing platform technology, delivery platform technology or product candidates or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our personnel from their normal responsibilities. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

***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 applications are due to be paid to the USPTO and foreign patent agencies outside of the United States over the lifetime of our owned or licensed patents and applications. In certain circumstances, we rely on our licensing partners to pay these fees due to U.S. and non-U.S. patent agencies. The USPTO and foreign patent agencies require compliance with several procedural, documentary, fee payment, and other similar provisions during the patent application process. We are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. While 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 a partial or complete loss of patent rights in the relevant jurisdiction. Were a noncompliance event to occur, our competitors might be able to enter the market with similar or identical products or technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.



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

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

Changes in either the patent laws or interpretation of the patent laws could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of our issued patents. For example, in March 2013, under the Leahy-Smith America Invents Act, or the America Invents Act, the United States transitioned from a “first to invent” to a “first-to-file” patent system. Under a “first-to-file” system, assuming that other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on an invention regardless of whether another inventor had made the invention earlier. A third party that files a patent application in the USPTO after March 2013, but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we or our licensors were the first to either file any patent application related to our technology or product candidates or invent any of the inventions claimed in our or our licensor’s patents or patent applications. The America Invents Act also includes a number of other significant changes to U.S. patent law, including provisions that affect the way patent applications are prosecuted, allowing third party submission of prior art and establish a new post-grant review system including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. The effects of some of these changes are currently unclear as the USPTO continues to promulgate new regulations and procedures in connection with the America Invents Act. In addition, the courts have yet to address many of these provisions and the applicability of the act and new regulations on the specific patents discussed in this filing have not been determined and would need to be reviewed. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

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

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

Patents have a limited lifespan. The terms of individual patents depend upon the legal term for patents in the countries in which they are granted. In most countries, including the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest non-provisional filing date in the applicable country. However, the actual protection afforded by a patent varies from country to country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. Various extensions including PTE and PTA, may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting our product candidates might expire before or shortly after we or our partners commercialize those candidates. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our U.S. patents may be eligible for limited PTE under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments. The Hatch-Waxman Amendments PTE term of up to five years as compensation for patent term lost during the FDA regulatory review process. A PTE cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent per product may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, even if we were to seek a PTE, it may not be granted because of, for example, the failure to exercise due diligence during the testing phase or regulatory review process, the failure to apply within applicable deadlines, the failure to apply prior to expiration of relevant patents, or any other failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain PTE or term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations, and prospects could be materially harmed.

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

In addition to seeking patents for our technology and product candidates, we also rely on know-how and trade secret protection, as well as confidentiality agreements, non-disclosure agreements and invention assignment agreements with our employees, consultants and third parties, to protect our confidential and proprietary information, especially where we do not believe patent protection is appropriate or obtainable.

It is our policy to require our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed by or made known to the individual or entity during the course of the party's relationship with us is to be kept confidential and not disclosed to third parties, except in certain specified circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and that are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property. In the case of consultants and other third parties, the agreements provide that all inventions conceived in connection with the services provided are our exclusive property. However, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Additionally, 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. Any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time-consuming, and the outcome is unpredictable.

In addition to contractual measures, we try to protect the confidential nature of our proprietary information through other appropriate precautions, such as physical and technological security measures. However, trade secrets and know-how can be difficult to protect. These measures may not, for example, in the case of misappropriation of a trade secret by an employee or third party with authorized access, provide adequate protection for our proprietary information. Our security measures may not prevent an employee or consultant from misappropriating our trade secrets and providing them to a competitor, and any recourse we might take against this type of misconduct may not provide an adequate remedy to protect our interests fully. In addition, trade secrets may be independently developed by others in a manner that could prevent us from receiving legal recourse. If any of our confidential or proprietary information, such as our trade secrets, were to be disclosed or misappropriated, or if any of that information was independently developed by a competitor, our competitive position could be harmed.

In addition, some courts inside and outside the United States are sometimes less willing or unwilling to protect trade secrets. If we choose to go to court to stop a third party from using any of our trade secrets, we may incur substantial costs. Even if we are successful, these types of lawsuits may consume our time and other resources. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

***Third parties may assert that our employees, consultants, or advisors have wrongfully used or disclosed confidential information or misappropriated trade secrets.***

As is common in the biotechnology and pharmaceutical industries, we employ individuals that are currently or were previously employed at universities, research institutions 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 we or these individuals have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Also, we have in the past and may in the future be subject to claims that these individuals are violating non-compete agreements with their former employers. We may then have to pursue litigation to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and, if securities analysts or investors perceive these results to be negative, that perception could have a substantial adverse effect on the price of our common stock. This type of litigation or proceeding could substantially increase our operating losses and reduce our resources available for development activities, and we may not have sufficient financial or other resources to adequately conduct this type of litigation or proceedings. For example, some of our competitors may be able to sustain the costs of this type of litigation or proceedings more effectively than we can because of their substantially greater financial resources. In any case, uncertainties resulting from the initiation and continuation of intellectual property litigation or other intellectual property related proceedings could adversely affect our ability to compete in the marketplace.

***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.***

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors or other 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 and could adversely affect our business, financial condition, results of operations and growth 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:

- any product candidates we may develop will eventually become commercially available in generic or biosimilar product forms;
- others may be able to make gene therapy products that are similar to any product candidates we may develop or utilize similar base editing technology but that are not covered by the claims of the patents that we license or may own 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 license or may own 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;
- we, or our license partners or current or future collaborators, may fail to meet our obligations to the U.S. government regarding any in-licensed patents and patent applications funded by U.S. government grants, leading to the loss or unenforceability of patent rights;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending, owned or licensed patent applications or those that we may own in the future will not lead to issued patents;

- it is possible that there are prior public disclosures that could invalidate our owned or in-licensed patents, or parts of our owned or in-licensed patents;
- it is possible that there are unpublished applications or patent applications maintained in secrecy that may later issue with claims covering our product candidates or technology similar to ours;
- it is possible that our owned or in-licensed patents or patent applications omit individual(s) that should be listed as inventor(s) or include individual(s) that should not be listed as inventor(s), which may cause these patents or patents issuing from these patent applications to be held invalid or unenforceable;
- issued patents that we hold rights to may be held invalid, unenforceable, or narrowed in scope, including as a result of legal challenges by our competitors;
- the claims of our owned or in-licensed issued patents or patent applications, if and when issued, may not cover our product candidates;
- the laws of foreign countries may not protect our proprietary rights or the proprietary rights of license partners or current or future collaborators to the same extent as the laws of the United States;
- the inventors of our owned or in-licensed patents or patent applications may become involved with competitors, develop products or processes that design around our patents, or become hostile to us or the patents or patent applications on which they are named as inventors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we have engaged in scientific collaborations in the past and will continue to do so in the future and our collaborators may develop adjacent or competing products that are outside the scope of our patents;
- we may not develop additional proprietary technologies that are patentable;
- any product candidates we develop may be covered by third parties' patents or other exclusive rights;
- the patents of others may harm our business; or
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

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

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

##### ***Regulatory requirements governing genetic medicines, and in particular any novel genetic medicines we may develop, have changed frequently and may continue to change in the future.***

Regulatory requirements governing genetic and cellular medicines, and in particular any novel genetic medicine products we may develop, have changed frequently and may continue to change in the future. We are aware of a limited number of genetic medicines that have received marketing authorization from the FDA and EMA. Even with respect to more established products in the genetic medicine 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 CBER to consolidate the review of genetic medicines and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER on its review. Genetic medicine 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, or EU. 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 genetic medicinal candidate that is submitted to the CHMP before CHMP adopts its final opinion. In the EU, the development and evaluation of a genetic medicinal product must be considered in the context of the relevant EU guidelines. The EMA may issue new guidelines concerning the development and marketing authorization for genetic medicinal products and require that we comply with these new guidelines. As a result, the procedures and standards applied to genetic medicines 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, including T-cell acute lymphoblastic leukemia, glycogen storage disorder and Stargardt disease, have small patient populations, making development of large and rigorous clinical trials more difficult. Further, even if we do achieve the pre-specified criteria, we may produce results that are unpredictable or inconsistent with the results of the non-primary endpoints or other relevant data. The FDA also weighs the benefits of a product against its risks, and the FDA may view the efficacy results in the context of safety as not being supportive of regulatory approval. Other regulatory authorities in the EU and other countries may make similar comments with respect to these endpoints and data. Any product candidates we may develop will be based on a novel technology that makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval. No gene editing therapeutic product has been approved in the United States or in Europe.

Adverse developments in post-marketing experience or in clinical trials conducted by others of genetic medicines 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 genetic medicinal 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 genetic medicine 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 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, recordkeeping, labeling, storage, approval, advertising, promotion, sale, import, export, and distribution, are subject to comprehensive regulation by the FDA, the EMA and other regulatory authorities in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third parties to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biological product candidate's safety, purity, and potency. Securing regulatory approval also requires the submission of extensive information about the product manufacturing process, and inspection of manufacturing facilities by the relevant regulatory authority. Any product candidates we develop may not be effective, may be only moderately effective, or may prove to have undesirable or unintended side effects, toxicities, or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

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

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

***Failure to obtain marketing approval in foreign jurisdictions would prevent any product candidates we 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 EU and other foreign jurisdictions, we or our third-party collaborators must obtain separate marketing approvals (a single one for the EU) 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 candidate be approved for reimbursement before the product candidate 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.

On June 23, 2016, the electorate in the U.K. voted in favor of leaving the EU, commonly referred to as Brexit. Following protracted negotiations, the U.K. left the EU on January 31, 2020 and a transition period to December 31, 2020, was established to allow the U.K. and the EU to negotiate the U.K.'s withdrawal. As a result, effective January 1, 2021, the U.K. is no longer part of the European Single Market and European Union Customs Union. A co-operation agreement was signed between the U.K. and the EU in December 2020 which has been applied provisionally since January 1, 2021 until it is ratified by all parties to that agreement. The agreement addresses trade, economic arrangements, law enforcement, judicial cooperation and a governance framework including procedures for dispute resolution, among other things. As both parties continue to work on the rules for implementation, significant political and economic uncertainty remains about how the precise terms of the relationship between the parties will differ from the terms before withdrawal.

Since the regulatory framework for pharmaceutical products in the U.K. covering the quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, the consequences of Brexit and the impact the future regulatory regime that applies to products and the approval of product candidates in the U.K. remains unclear. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will continue to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law of the body of EU law instruments governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the U.K. for our product candidates, which could significantly and materially harm our business.

***Even if we, or any collaborators we may have, obtain marketing approvals for any product candidates we develop, the terms of approvals and ongoing regulation of our product candidates could require the substantial expenditure of resources and may limit how we, or they, manufacture and market our product candidates, 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, EMA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, facility registration and drug 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. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine.

Accordingly, assuming we, or any collaborators we may have, receive marketing approval for one or more product candidates we develop, we, and such collaborators, and our and their contract manufacturers will continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance, and quality control. If we and such collaborators are not able to comply with post-approval regulatory requirements, we and such collaborators could be subject to enforcement actions or 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.

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

The FDA, the EMA, and other regulatory agencies closely regulate the post-approval marketing and promotion of medicines to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA, the EMA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we market our medicines for off-label use, we may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the Department of Justice. Violation of the Federal Food, Product, and Cosmetic Act and other statutes, including the False Claims Act, and equivalent legislation in other countries relating to the promotion and advertising of prescription products may also lead to investigations or allegations of violations of federal and state and other countries' health care fraud and abuse laws and state consumer protection laws. Even if it is later determined we were not in violation of these laws, we may be faced with negative publicity, incur significant expenses defending our actions and have to divert significant management resources from other matters.

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 negative consequences, 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;
- restrictions on future procurements with governmental authorities;
- 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 may develop and adversely affect our business, financial condition, results of operations, and prospects.

***Fast track, breakthrough, or regenerative medicine advanced therapy designation by the FDA may not actually lead to a faster development or regulatory review or approval process and does not assure FDA approval of any product candidates we may develop.***

FDA's fast track, breakthrough, and regenerative medicine advanced therapy, or RMAT, programs are intended to expedite the development of certain qualifying products intended for the treatment of serious diseases and conditions. If a product candidate is intended for the treatment of a serious or life-threatening condition and preclinical or clinical data demonstrate the product's potential to address an unmet medical need for this condition, the sponsor may apply for FDA fast track designation. A product candidate may be designated as a breakthrough therapy if it is intended to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. A product candidate may receive RMAT designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening condition, and preliminary clinical evidence indicates that the product candidate has the potential to address an unmet medical need for such condition. While we may seek fast track, breakthrough, and/or RMAT designation, there is no guarantee that we will be successful in obtaining any such designation. Even if we do obtain such designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. A fast track, breakthrough, or RMAT designation does not ensure that the product candidate will receive marketing approval or that approval will be granted within any particular timeframe. In addition, the FDA may withdraw fast track, breakthrough, or RMAT designation if it believes that the designation is no longer supported by data from our clinical development program. Fast track, breakthrough, and/or RMAT designation alone do not guarantee qualification for the FDA's priority review procedures.

***Priority review designation by the FDA may not lead to a faster regulatory review or approval process and, in any event, does not assure FDA approval of any product candidates we may develop.***

If the FDA determines that a product candidate is intended to treat a serious disease or condition and, if approved, would provide a significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of such disease or condition, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review a marketing application is six months from filing of the application, rather than the standard review period of ten months. We may request priority review for certain of our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may disagree and decide not to grant it. Moreover, a priority review designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or thereafter.



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

In the EU, we may seek PRIME designation for some of our product candidates in the future. PRIME is a voluntary program aimed at enhancing the EMA's role to reinforce scientific and regulatory support in order to optimize development and enable accelerated assessment of new medicines that are of major public health interest with the potential to address unmet medical needs. The program focuses on medicines that target conditions for which there exists no satisfactory method of treatment in the EU or even if such a method exists, it may offer a major therapeutic advantage over existing treatments. PRIME is limited to medicines under development and not authorized in the EU and where the applicant intends to apply for an initial marketing authorization application through the centralized procedure. To be accepted for PRIME, a product candidate must meet the eligibility criteria in respect of its major public health interest and therapeutic innovation based on information that is capable of substantiating the claims. The benefits of a PRIME designation include the appointment of a CHMP rapporteur to provide continued support and help to build knowledge ahead of a marketing authorization application, early dialogue and scientific advice at key development milestones, and the potential to qualify products for accelerated review, meaning reduction in the review time for an opinion on approvability to be issued earlier in the application process. PRIME enables an applicant to request parallel EMA scientific advice and health technology assessment advice to facilitate timely market access. Even if we receive PRIME designation for any of our product candidates, the designation may not result in a materially faster development process, review or approval compared to conventional EMA procedures. Further, obtaining PRIME designation does not assure or increase the likelihood of EMA's grant of a marketing authorization.

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

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

Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates 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 and the SEC, have had to furlough critical FDA, SEC and other government 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. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Separately, in response to the COVID-19 pandemic, since March 2020 when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. The FDA has developed a rating system to assist in determining when and where it is safest to conduct prioritized domestic inspections. As of May 2021, certain inspections, such as foreign preapproval, surveillance, and for-cause inspections that are not deemed mission-critical, remain temporarily postponed. In April 2021, the FDA issued guidance for industry formally announcing plans to employ remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates and in May 2021 announced plans to continue progress toward resuming standard operational levels. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the FDA has stated that it generally intends to issue a complete response letter or defer action on the application until an inspection can be completed.

In 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the ongoing COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to continue its current pace and review timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspections during the review period. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown or other disruption 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. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets.

***We may not be able to obtain orphan drug exclusivity for one or more of our product candidates, 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 candidate 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 product candidates by the EMA in the EU. Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for another product candidate for the same orphan therapeutic indication for that time period. The applicable period is seven years in the United States and ten years in the EU. The exclusivity period in the EU 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.

The FDA's standards for granting orphan drug exclusivity in the gene therapy context are unclear and evolving. For example, in September 2021, the FDA issued final guidance describing its current thinking on when a gene therapy product is the "same" as another product for purposes of orphan exclusivity. Under the guidance, if either the transgene or vector differs between two gene therapy products in a manner that does not reflect "minor" differences, the two products would be considered different drugs for orphan drug exclusivity purposes. The FDA will determine whether two vectors from the same viral class are the same on a case-by-case basis and may consider additional key features in assessing sameness. In addition, in order for the FDA to grant orphan drug exclusivity to one of our product candidates, the agency must find that the product candidate is indicated for the treatment of a condition or disease 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 the product candidate available for the disease or condition will be recovered from sales of the product 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 candidate, that exclusivity may not effectively protect the product candidate from competition because different product candidates can be approved for the same condition. 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 addition, even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later product candidate is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care compared with the product that has orphan exclusivity.

On August 3, 2017, the Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. Further, under Omnibus legislation signed in December 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.

The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. This may be particularly true in light of a decision from the Court of Appeals for the 11<sup>th</sup> Circuit in September 2021 finding that, for the purpose of determining the scope of exclusivity, the term "same disease or condition" means the designated "rare disease or condition" and could not be interpreted by the agency to mean the "indication or use." Thus, the court concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." 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.

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

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

- federal false claims, false statements and civil monetary penalties laws prohibiting, among other things, any person from knowingly presenting, or causing to be presented, a false claim for payment of government funds or knowingly making, or causing to be made, a false statement to get a false claim paid;
- federal healthcare program anti-kickback law, which prohibits, among other things, persons from offering, soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual for, or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which, in addition to privacy protections applicable to healthcare providers and other entities, prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- the federal Food, Drug, and Cosmetic Act, or the FDCA, which among other things, strictly regulates drug marketing, prohibits manufacturers from marketing such products for off-label use and regulates the distribution of samples;
- federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs;
- the so-called “federal sunshine” law under the Healthcare Reform Act, which requires pharmaceutical and medical device companies to monitor and report certain financial interactions with certain healthcare providers to the Center for Medicare & Medicaid Services within the U.S. Department of Health and Human Services for re-disclosure to the public, as well as ownership and investment interests held by physicians, other healthcare providers and their immediate family members;
- state laws also requiring pharmaceutical companies to comply with specific compliance standards, restrict financial interactions between pharmaceutical companies and healthcare providers or require pharmaceutical companies to report information related to payments to health care providers or marketing expenditures; and
- analogous state and foreign laws and regulations, such as state anti-kickback, anti-bribery and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. Given the breadth of the laws and regulations, limited guidance for certain laws and regulations and evolving government interpretations of the laws and regulations, governmental authorities may possibly conclude that our business practices may not comply with healthcare laws and regulations. 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 health care 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.

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 EU. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of EU Member States, such as the U.K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU 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 EU Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

***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 the 2010 Patient Protection and Affordable Care Act, or the 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 2031 with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 unless additional Congressional Action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. 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. The U.S. Supreme Court heard this case on November 10, 2020 and, on June 17, 2021, dismissed this action after finding that the plaintiffs do not have standing to challenge the constitutionality of the PPACA. Litigation and legislation over the PPACA are likely to continue, with unpredictable and uncertain results.

In January 2021, a new executive order directed 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 the COVID-19 pandemic; 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. For example, on September 24, 2020, a rulemaking was finalized that allows 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).

In addition, in prior administrations, several executive orders intended to lower the costs of prescription drug products were issued. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing a most favored nation model, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries effective January 1, 2021, but such final rule is subject to a nationwide preliminary injunction for its failure to comply with notice and comment rulemaking requirements. The current administration has frozen certain of the previous administration's measures to reform drug prices, pending further review. Further, Executive Order 14063, signed on July 9, 2021, focuses on, among other things, the price of pharmaceuticals. To address these costs, the Order directs the Department of Health and Human Services, or HHS, to create a plan within 45 days to combat "excessive pricing of prescription drugs and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such drugs, and to address the recurrent problem of price gouging."

On September 9, 2021, HHS released its plan to reduce drug prices. The key features of that plan are to: (a) make drug prices more affordable and equitable for all consumers and throughout the health care system by supporting drug price negotiations with manufacturers; (b) improve and promote competition throughout the prescription drug industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments. Further, on August 21, 2021, in response to the litigation challenging the most favored nation model, CMS issued a proposed rule to rescind the interim final rule, following public notice and comment. With issuance of this proposal, CMS stated that it will carefully consider the comments it received on the November 2020 interim final rule as it explores all options to incorporate value into payments for Medicare Part B drugs and improve beneficiaries' access to evidence-based care.

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.

In the EU, 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 EU, 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 EU, 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 commercial 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 EU and other jurisdictions, provide accurate information to the FDA, the EMA, 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, the EMA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations, and prospects, including the imposition of significant fines or other sanctions.

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

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

The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business from paying, offering, authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring us 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.

Similarly, the U.K. Bribery Act 2010 has extra-territorial effect for companies and individuals having a connection with the U.K. The U.K. Bribery Act prohibits inducements both to public officials and private individuals and organizations. Compliance with the FCPA and the U.K. Bribery Act is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA 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. 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 and contractual obligations could adversely affect our business.***

We are subject to a wide variety of 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, including comprehensive regulatory systems in the U.S., EU and U.K. and other countries around the world. 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, imprisonment of company officials and public censure, 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. In addition, these laws and regulations may impose additional costs on our business activities, including costs of contracting with vendors and other business partners and the costs of identifying appropriate patients for clinical trials or subsequent treatment.

If we are unable to properly protect the privacy and security of individually identifiable health information, we could be found to have breached our contracts. Further, if we fail to comply with applicable privacy laws, we could face civil and criminal penalties or other enforcement risks related to our business. In addition to these potential penalties, 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.

While we continue to address the implications of the recent changes to data privacy regulations, data privacy remains an evolving landscape at both the domestic and international level, with new regulations coming into effect and continued legal challenges, and our efforts to comply with the evolving data protection rules may be unsuccessful. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices. We must devote significant resources to understanding and complying with this changing landscape. Failure to comply with laws regarding data protection would expose us to risk of enforcement actions taken by data protection authorities in the EEA and elsewhere and carries with it the potential for significant penalties if we are found to be non-compliant. Similarly, failure to comply with federal and state laws in the United States regarding privacy and security of personal information could expose us to 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. 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 business, financial condition, results of operations or prospects.

***Social media platforms present new risks and challenges to our business.***

As social media continues to expand, it also presents us with new risks and challenges. Social media is increasingly being used to communicate information about us, our programs and the diseases our product candidates are being developed to treat. Social media practices in the pharmaceutical and biotechnology industries are evolving, which creates uncertainty and risk of noncompliance with regulations applicable to our business. For example, patients may use social media platforms to comment on the effectiveness of, or adverse experiences with, a product or a product candidate, which could result in reporting obligations or other consequences. Further, the accidental or intentional disclosure of non-public information by our workforce or others through media channels could lead to information loss. In addition, there is a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us, our products, or our product candidates on any social media platform. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business including quick and irreversible damage to our reputation, brand image and goodwill.

## **Risks related to employee matters, managing growth and information technology**

***Our future growth may depend on our ability to identify and acquire businesses or technologies, and if we do not successfully do so, or otherwise fail to integrate any new businesses or technologies into our operations, we may have limited growth opportunities and it could result in significant impairment charges or other adverse financial consequences.***

We are continuing to seek to acquire businesses or technologies that we believe are a strategic fit with our business strategy. Future acquisitions, however, may entail numerous operational and financial risks, including:

- a reduction of our current financial resources;
- incurrence of substantial debt or dilutive issuances of securities to pay for acquisitions and in connection with future milestone payment obligations under such acquisition agreements;
- difficulty or inability to secure financing to fund development activities for those acquired or in-licensed technologies;
- higher than expected acquisition and integration costs;
- disruption of our business, customer base and diversion of our management's time and attention to develop acquired technologies; and
- exposure to unknown liabilities.

We may not have sufficient resources to identify and execute the acquisition businesses and technologies and integrate them into our current infrastructure. In particular, we may compete with larger biotechnology companies and other competitors in our efforts to establish new collaborations and in-licensing opportunities. These competitors likely will have access to greater financial resources than we do and may have greater expertise in identifying and evaluating new opportunities. Furthermore, there may be overlap between our product candidates and the companies which we acquire that may create conflicts in relationships or other commitments detrimental to the integrated businesses. Additionally, the time between our expenditures to acquire or in-license new technologies or businesses and the subsequent generation of revenues from those acquired technologies or businesses (or the timing of revenue recognition related to licensing agreements and/or strategic collaborations) could cause fluctuations in our financial performance from period to period. Finally, if we devote resources to potential acquisition opportunities that are never completed, or if we fail to realize the anticipated benefits of those efforts, we could incur significant impairment charges or other adverse financial consequences.

***Our future success depends on our ability to retain our Chief Executive Officer, President and Chief Scientific Officer, other key executives and to attract, retain, and motivate qualified personnel.***

We are highly dependent on John Evans, our Chief Executive Officer, and Dr. Giuseppe Ciaramella, our President and Chief Scientific Officer, as well as the other principal members of our management and scientific teams. Mr. Evans, Dr. Ciaramella and such other principal members are employed "at will," meaning we or they may terminate the employment at any time. We do not maintain "key person" insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development, and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing, and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these 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, including our scientific co-founders, 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. The inability to recruit, or loss of services of certain executives, key employees, consultants, or advisors, may impede the progress of our research, development, and commercialization objectives and have a material adverse effect on our business, financial condition, results of operations, and prospects.

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

In connection with the growth and advancement of our pipeline, we expect to increase the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, and sales and marketing. 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 expected expansion of our operations or recruit and train additional qualified personnel. Moreover, the expected physical 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.

#### **Risks related to our common stock**

***The market price of our common stock may be volatile and fluctuate substantially, which could result in substantially losses for purchasers of our common stock and subject us to securities class action litigation.***

Our stock price has been, and in the future, may be, subject to substantial volatility. The stock market in general, and the market for 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, you may not be able to sell your common stock at or above your initial purchase price. The market price for our common stock may be influenced by many factors, including:

- the success of existing or new competitive product candidates or technologies;
- the timing and results of preclinical studies and clinical trials for any product candidates that we develop;
- failure or discontinuation of any of our product development and research programs;
- results of preclinical studies, clinical trials, or regulatory approvals of product candidates of our competitors, or announcements about new research programs or product candidates of our competitors;
- developments or changing views regarding the use of genetic medicines, including those that involve gene editing;
- commencement or termination of collaborations for our product development and research programs;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our research programs, clinical development programs, or product candidates that we may develop;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines, or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- expiration of any future market stand-off or lock-up agreements;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- the effects of pandemics and public health emergencies, including the ongoing COVID-19 pandemic;
- general economic, industry, and market conditions; and
- the other factors described in this “Risk Factors” section.

Following periods of such volatility in the market price of a company's securities, securities class action litigation has often been brought against that company. Because of the potential volatility of our stock price, we may become the target of securities litigation in the future. Securities litigation could result in substantial costs and divert management's attention and resources from our business.

***If we fail to establish and maintain proper and effective internal control over financial reporting, our operating results and our ability to operate our business could be harmed.***

Maintaining adequate internal financial and accounting controls and procedures to ensure that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that needs to be re-evaluated frequently. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles. To comply with the requirements of being a public company, we have undertaken certain actions, such as documenting, reviewing and improving our internal controls and procedures for compliance with Section 404 of the Sarbanes-Oxley Act of 2002, or SOX, which requires annual management assessment of the effectiveness of our internal control over financial reporting and an annual report on and attestation to such assessment by our registered public accounting firm. Notwithstanding such actions, we may not be effective in maintaining the adequacy of our internal controls, and any failure to maintain that adequacy, or consequent inability to produce accurate financial statements on a timely basis, or any disagreement with our auditors on whether we have maintained such adequacy, could increase our operating costs and harm our business. In addition, investors' perceptions that our internal controls are inadequate or that we are unable to produce accurate financial statements on a timely basis may harm our common stock price and make it more difficult for us to effectively market and sell our service to new and existing customers.

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

As a public company, we have incurred and expect to continue to incur significant legal, accounting, and other expenses. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Stock 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 a substantial amount of time towards maintaining compliance with these requirements. These requirements have increased our legal and financial compliance costs and make some activities more time-consuming and costly. For example, as a public company it is more difficult and more expensive for us to maintain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our board of directors. 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.

***We do not expect to pay any dividends for the foreseeable future. Investors may never obtain a return on their investment unless they sell our common stock for a price higher than which they paid for it.***

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our existing operations. In addition, any future credit facility may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment.

***Provisions in our amended and restated certificate of incorporation, our amended and restated by-laws and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.***

Our amended and restated certificate of incorporation, amended and restated by-laws and Delaware law contain provisions that may have the effect of discouraging, delaying or preventing a change in control of us or changes in our management that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. Our amended and restated certificate of incorporation and by-laws, include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;

- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- provide that our directors may be removed only for cause;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorized our board of directors to make, alter, amend or repeal our amended and restated by-laws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated by-laws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management. These provisions could also limit the price that investors might be willing to pay for shares of our common stock, thereby depressing the market price of our common stock.

In addition, because we are incorporated in the State of Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, 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.

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

***Our amended and restated certificate of incorporation and amended and restated by-laws designate the state or federal courts within the State of Delaware as the exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.***

Our amended and restated certificate of incorporation provides that, subject to limited exceptions, the state or federal courts within the State of Delaware will be exclusive forums for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (3) any action asserting a claim against us arising pursuant to any provision of the DGCL, our amended and restated certificate of incorporation or our amended and restated by-laws, (4) any action to interpret, apply, enforce or determine the validity of our amended and restated certificate of incorporation or our amended and restated by-laws or (5) any other action asserting a claim against us that is governed by the internal affairs doctrine. Furthermore, our amended and restated by-laws also provide that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation and amended and restated by-laws described above. These choice of forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and employees. Alternatively, if a court were to find these provisions of our amended and restated certificate of incorporation or amended and restated by-laws inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business and financial condition. For example, the Court of Chancery of the State of Delaware recently determined that a provision stating that federal district courts of the United States are the exclusive forum for resolving any complaint asserting a cause of action under the Securities Act is not enforceable. However, this decision may be reviewed and ultimately overturned by the Delaware Supreme Court.

#### **General risk factors**

##### ***Public health epidemics or outbreaks, including COVID-19, could adversely impact our business.***

Due to the evolving and uncertain global impacts of the COVID-19 pandemic, we cannot precisely determine or quantify the impact this pandemic will have on our business operations. The extent to which COVID-19 may impact our business, results of operations and future growth prospects will depend on a variety of factors and future developments, which are highly uncertain and cannot be predicted with confidence, including the duration, scope and severity of the pandemic, the duration and extent of travel restrictions and social distancing in the U.S. and other countries, business closures or business disruptions, the effectiveness of actions taken in the U.S. and other countries to contain and treat COVID-19, periodic spikes in infection rates, new strains of the virus that causes outbreaks of COVID-19, and the broad availability of effective vaccines and therapeutics.

The rapid spread of the virus and variant strains has led to the implementation of various responses, including government-imposed quarantines, including shelter-in-place mandates, sweeping restrictions on travel, and other public health safety measures, as well as reported adverse impacts on healthcare resources, facilities and providers, in Massachusetts, where our primary offices and laboratory spaces are located, across the United States, and in other countries. The extent to which COVID-19 continues to impact our operations and those of our third-party partners will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration of the outbreak, availability of effective vaccines and therapeutics, additional or modified government actions, new virus variants and the actions taken to contain COVID-19 or treat its impact, among others. As interventions to contain the spread of the virus are lifted or reduced, new COVID-19 outbreaks may result in new or heightened restrictions.

To protect the health of our employees and their families, and our communities, in accordance with direction from state and local government authorities, we have in the past restricted access to our facilities to personnel and third parties who must perform critical activities that must be completed on-site, limited the number of personnel that can be present at our facilities at any one time, and requested that some of our personnel work remotely. We may reinstitute similar restrictions in the future in accordance with federal, state and local requirements. In the event that governmental authorities were to increase current restrictions, our employees conducting research and development, or manufacturing activities may not be able to access our laboratory or manufacturing space, and our core activities may be significantly limited or curtailed, possibly for an extended period of time.

The COVID-19 pandemic has also impacted, and may continue to impact, our third-party suppliers, 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 components. While we maintain an inventory of materials necessary to conduct our preclinical studies and upcoming clinical trial, a prolonged outbreak could lead to shortages in these materials.

Additionally, timely completion of preclinical activities and clinical trials is dependent upon the availability of, for example, preclinical and clinical trial sites, researchers and investigators, regulatory agency personnel, and materials, which may be adversely affected by global health matters, such as pandemics. We plan to conduct preclinical activities for our programs and clinical trials in geographies which are currently being affected by COVID-19.

Some factors from the COVID-19 pandemic that could delay or otherwise adversely affect the completion of our preclinical and clinical activities and, depending on the duration of the outbreak, the initiation of any future clinical trials, as well as our business generally, include:

- business disruptions caused by potential workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments and operations, staffing shortages, travel limitations, cyber security and data accessibility, or communication or mass transit disruptions, any of which could adversely impact our business operations or delay necessary interactions with local regulators, ethics committees, manufacturing sites, research sites and other important agencies and contractors;
- limitations on our business operations by local, state, or the federal government that could impact our ability to conduct our preclinical and clinical activities, including completing additional IND-enabling studies;
- limitations on travel that could hinder our timelines;
- interruption in global shipping affecting the transport of key materials; and
- interruption of, or delays in receiving, key materials from our CMOs due to staffing shortages, production slowdowns or stoppages, increased demand from third parties for key materials related to COVID-19 research and vaccine development and disruptions in delivery systems.

These and other factors arising from COVID-19 could worsen in countries that are already afflicted with COVID-19 or could continue to spread to additional countries, each of which could further adversely impact our ability to conduct preclinical studies or clinical trials, and, in general, our business, and could have a material adverse impact on our operations and financial condition and results.

Additionally, the future impact of the COVID-19 pandemic on our stock price and other biopharmaceutical companies is uncertain and may make us look less attractive to investors and, as a result, there may be a less active trading market for our common stock, our stock price may be more volatile, and our ability to raise capital could be impaired.

The COVID-19 pandemic continues to rapidly evolve. The extent to which the outbreak may impact our business, preclinical studies and clinical trials will highly depend on future developments, which are very uncertain and cannot be predicted with confidence, such as the duration of the outbreak, travel restrictions and other actions to contain the outbreak or address its impact, such as social distancing and quarantines or lockdowns in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and address the disease.

The COVID-19 pandemic may also have the effect of heightening many of the other risks described in this section titled “Item 1A. Risk Factors,” such as risks related to our need to raise additional funding, fluctuation of our quarterly financial results, and our ability to obtain and maintain regulatory approvals.

***Comprehensive tax reform legislation could adversely affect our business and financial condition.***

On December 22, 2017, the Tax Act was signed into law. The Tax Act, as amended by the CARES Act, among other things, contains significant changes to corporate taxation, including (i) reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, (ii) limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), (iii) limitation of the deduction for NOLs to 80% of current year taxable income in respect of NOLs generated during or after 2018 and elimination of NOL carrybacks for NOLs generated on or after January 1, 2021, (iv) immediate deductions for certain new investments instead of deductions for depreciation expense over time, and (v) modification or repeal of many business deductions and credits. Any federal NOL incurred in 2018 and in future years may now be carried forward indefinitely pursuant to the Tax Act. Similar rules and limitations may apply for state income tax purposes.

In addition to the Tax Act, as part of Congress' response to the COVID-19 pandemic, economic relief legislation was enacted in 2020 and 2021 containing tax provisions, including the CARES Act. Regulatory guidance under the Tax Act and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen their impact on our business and financial condition. Also, as a result of the changes in the U.S. presidential administration and control of the U.S. Senate in 2021, additional tax legislation may be enacted; any such additional legislation could have an impact on us. In addition, it is uncertain if and to what extent various states will conform to the Tax Act and additional tax legislation.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. A severe or prolonged economic downturn, or additional global financial crises, could result in a variety of risks to our business, including weakened demand for our product candidates, if approved, or 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. 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.

***If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.***

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline. Moreover, if any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model or our stock performance, or if our operating results fail to meet the expectations of the investor community, one or more of the analysts who cover our company may change their recommendations regarding our company, and our stock price could decline.

***Our internal computer systems, or those of our third-party vendors, collaborators or other contractors or consultants, may fail or suffer security breaches, 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.***

Our internal computer systems and those of our current and any future third-party vendors, collaborators and other contractors or consultants 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. While we seek to protect our information technology systems from system failure, accident and security breach through our information security program and relevant contractual agreements with our business partners, 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 information or other disruptions, including the possible loss of personal data. 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, as well as subject us to obligations and risks related to the potential loss of personal 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 to potential costs related to regulatory investigations in the United States or other countries. In addition, our remediation efforts may not be successful. If we do not allocate and effectively manage the resources necessary to build and sustain the proper technology and cybersecurity infrastructure, we could suffer significant business disruption, including transaction errors, supply chain or manufacturing interruptions, processing inefficiencies, data loss or the loss of or damage to intellectual property or other proprietary information.

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, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed. Any of the above could have a material adverse effect on our business, financial condition, results of operations or prospects.

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

None.

**Item 2. Properties.**

We have leased approximately 38,203 square feet of office and laboratory space in Cambridge, Massachusetts under a lease that expires in October 2028 and approximately 130,258 square feet of office and laboratory space in Cambridge, Massachusetts under a lease that expires in 2034. Additionally, we entered into a lease agreement with Alexandria Real Estate Equities, Inc. to build a 100,000 square foot manufacturing facility in Research Triangle Park, North Carolina intended to support a broad range of clinical programs, which is currently under construction. We expect that the facility will be operational by the first quarter of 2023. Upon completion of construction and our commencement of our occupancy within the space, the lease will expire on the fifteenth anniversary of commencement and we have an option to extend the lease term for two five-year terms. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

**Item 3. Legal Proceedings.**

We are not currently a party to any material legal proceedings. From time to time, we may be subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Regardless of the outcome, litigation can have a material adverse effect on us because of defense and settlement costs, diversion of management resources, and other factors.

**Item 4. Mine Safety Disclosures.**

Not Applicable.

## PART II

### Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

#### Market information

Our common stock has been publicly traded on the Nasdaq Global Select Market under the symbol "BEAM" since February 6, 2020. Prior to that time, there was no public market for our common stock.

#### Holdings

As of February 22, 2022, there were approximately 38 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

#### Dividends

We have not declared or paid any cash dividends on our capital stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends to holders of common stock in the foreseeable future.

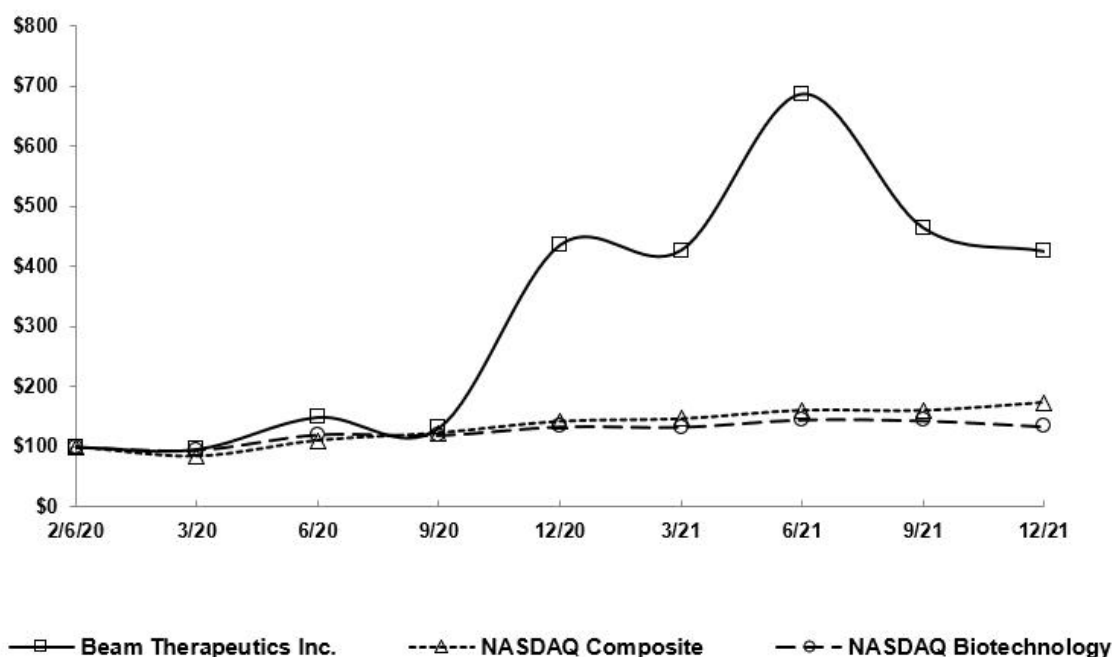
## Stock Performance Graph

The following performance graph and related information shall not be deemed to be “soliciting material” or to be “filed” with the Securities and Exchange Commission, or SEC, for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, nor shall such information be incorporated by reference into any future filing under the Exchange Act or Securities Act of 1933, as amended, or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The graph set forth below compares the cumulative total stockholder return on our shares of common stock between February 6, 2020 (the date of our initial public offering) and December 31, 2021, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of \$100 on February 6, 2020 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The graph uses the closing sales price of our common stock of \$18.75 per share on February 6, 2020 as the initial value of our common stock and not the initial offering price to the public of \$17.00 per share. The comparisons shown in the graph below are based upon historical data. The stock price performance included in this graph is not necessarily indicative of future stock price performance.

### COMPARISON OF 23 MONTH CUMULATIVE TOTAL RETURN\*

Among Beam Therapeutics Inc., the NASDAQ Composite Index  
and the NASDAQ Biotechnology Index



\*\$100 invested on 2/6/20 in stock or 1/31/20 in index, including reinvestment of dividends.  
Fiscal year ending December 31.



**Securities authorized for issuance under equity compensation plans**

Information about our equity compensation plans is incorporated herein by reference to Item 12, *Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters*, of this Annual Report on Form 10-K.

**Purchases of equity securities by the issuer or affiliated purchasers**

Neither we nor any affiliated purchaser or anyone acting on our behalf or on behalf of an affiliated purchaser made any purchases of shares of our common stock during the fourth quarter of 2021.

**Item 6. [Reserved]**

## 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 the related notes to those statements included elsewhere in this Annual Report on Form 10-K. In addition to historical financial information, the following discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. Some of the numbers included herein have been rounded for the convenience of presentation. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of many factors, including those discussed under Item 1A, Risk factors, in this Annual Report on Form 10-K.

### Overview

We are a biotechnology company committed to establishing the leading, fully integrated platform for precision genetic medicines. Our vision is to provide life-long cures to patients suffering from serious diseases. To achieve this vision, we have assembled a platform that includes a suite of gene editing and delivery technologies and are in the process of developing internal manufacturing capabilities. Our suite of gene editing technologies is anchored by our proprietary base editing technology, which potentially enables a differentiated class of precision genetic medicines that target a single base in the genome without making a double-stranded break in the DNA. This approach uses a chemical reaction designed to create precise, predictable and efficient genetic outcomes at the targeted sequence. Our proprietary base editors have two principal components: (i) a clustered regularly interspaced short palindromic repeats, or CRISPR, protein, bound to a guide RNA, that leverages the established DNA-targeting ability of CRISPR, but is modified to not cause a double-stranded break, and (ii) a base editing enzyme, such as a deaminase, which carries out the desired chemical modification of the target DNA base. We believe this design contributes to a more precise and efficient edit compared to traditional gene editing methods, which operate by creating targeted double-stranded breaks in the DNA that can result in unwanted DNA modifications. We believe that the precision of our editors will dramatically increase the impact of gene editing for a broad range of therapeutic applications.

To unlock the full potential of our base editing technology across a wide range of therapeutic applications, we are pursuing a broad suite of both clinically validated and novel delivery modalities, depending on tissue type, including: (1) electroporation for efficient delivery to blood cells and immune cells *ex vivo*; (2) lipid nanoparticles, or LNPs, for non-viral *in vivo* delivery to the liver and potentially other organs in the future; and (3) adeno-associated viral vectors, or AAV, for *in vivo* viral delivery to the eye and potentially other organs.

The elegance of the base editing approach combined with a tissue specific delivery modality provides the basis for a targeted efficient, precise, and highly versatile gene editing system, capable of gene correction, gene modification, gene silencing or gene activation, and/or multiplex editing of several genes simultaneously. We are currently advancing a broad, diversified portfolio of base editing programs against distinct editing targets, utilizing the full range of our development capabilities. We believe the flexibility and versatility of our base editors and delivery technologies may have broad therapeutic applicability and have the potential to transform the field of precision genetic medicines.

We believe that building an integrated platform combining our gene editing capabilities with advanced delivery and manufacturing capabilities will give us the flexibility to develop our own sustainable portfolio and to create a hub for partnering with other companies to unlock the full potential of precision genetic medicine across a broad array of possible applications.

### Manufacturing

To realize the full potential of base editors as a differentiated class of medicines and to enable our parallel investment strategy in multiple delivery modalities, we are building customized and integrated capabilities across discovery, manufacturing, and preclinical and clinical development. Due to the critical importance of high-quality manufacturing and control of production timing and know-how, we have taken steps toward establishing our own manufacturing facility, which will provide us the flexibility to manufacture a variety of different product modalities. We believe this investment will maximize the value of our portfolio and capabilities, the probability of technical success of our programs, and the speed at which we can provide potentially life-long cures to patients.

In August 2020, we entered into a lease agreement with Alexandria Real Estate Equities, Inc. to build a 100,000 square foot current cGMP compliant manufacturing facility in Research Triangle Park, North Carolina intended to support a broad range of clinical programs. The initial estimate of the minimum amount of undiscounted lease payments due under this lease is \$69.0 million. The tabular disclosure of minimum lease payments under Note 7, *Leases*, to our consolidated financial statements in this Annual Report on Form 10-K does not include payments due under this lease. We anticipate that the facility will be operational in the first quarter of 2023. The project is facilitated, in part, by a Job Development Investment Grant approved by the North Carolina Economic Investment Committee, which authorizes potential reimbursements based on new tax revenues generated through the project. The facility is designed to support manufacturing for our *ex vivo* cell therapy programs in hematology and oncology and *in vivo* non-viral delivery programs for liver diseases, with flexibility to support manufacturing of our viral delivery programs, and ultimately, scale-up to support potential commercial supply.

For our initial waves of clinical trials, we expect to use CMOs with relevant manufacturing experience in genetic medicines.

## Acquisitions

In February 2021, we acquired Guide Therapeutics, Inc., or Guide, for upfront consideration in an aggregate amount of \$120.0 million, excluding customary purchase price adjustments, in shares of our common stock, based upon the volume-weighted average price of the common stock over the ten trading-day period ending on February 19, 2021. In addition, Guide's former stockholders and optionholders are eligible to receive up to an additional \$100.0 million in technology milestone payments and \$220.0 million in product milestone payments, payable in our common stock.

## COVID-19

With the ongoing concerns related to the COVID-19 pandemic, during the year ended December 31, 2021, we maintained and expanded our business continuity plans to address and mitigate the impact of the COVID-19 pandemic on our business. We expect to continue incurring additional costs to ensure we adhere to the guidelines instituted by the Centers for Disease Control and to provide a safe working environment to our onsite employees.

The extent to which the COVID-19 pandemic impacts our business, our corporate development objectives, results of operations and financial condition, including the value of and market for our common stock, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the duration, scope and severity of the pandemic, the existence and duration of any travel restrictions or business restrictions in the United States and other countries, business closures and business disruptions, the effectiveness of actions taken in the United States and other countries to contain and treat the disease, periodic spikes in infection rates, new strains of the virus that cause outbreaks of COVID-19, and the broad availability of effective vaccines and therapeutics.

Disruptions to the global economy and supply chain, disruption of global healthcare systems, and other significant impacts of the COVID-19 pandemic could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

While the COVID-19 pandemic did not significantly impact our business or results of operations during the year ended December 31, 2021, the length and extent of the pandemic, its consequences, and containment efforts will determine its future impact on our operations and financial condition. For a more detailed discussion of risks related to COVID-19, please see Part II, Item 1A, *Risk factors—General risk factors*, in this Annual Report on Form 10-K.

## Financial operations overview

### General

We were founded in January 2017 and began operations in July 2017. Since our inception, we have devoted substantially all of our resources to building our base editing platform and advancing development of our portfolio of programs, establishing and protecting our intellectual property, conducting research and development activities, organizing and staffing our company, business planning, raising capital and providing general and administrative support for these operations. To date, we have financed our operations primarily through the sales of our redeemable convertible preferred stock, proceeds from offerings of our common stock and payments received under collaboration and license agreements.

We are an early-stage company, and all of our programs are at a preclinical or early clinical stage of development. To date, we have not generated any revenue from product sales and do not expect to generate revenue from the sale of products for the foreseeable future. Our revenue to date has been primarily derived from license and collaboration agreements with partners. Since inception we have incurred significant operating losses. Our net losses for the years ended December 31, 2021, 2020 and 2019 were \$370.6 million, \$194.6 million and \$78.3 million, respectively. As of December 31, 2021, we had an accumulated deficit of \$768.3 million. We expect to continue to incur significant expenses and increasing operating losses in connection with ongoing development activities related to our internal programs and collaborations as we continue our preclinical and clinical development of product candidates; advance additional product candidates toward clinical development; build and operate our cGMP facility in North Carolina; further develop our base editing platform; continue to make investments in delivery technology for our base editors, including the LNP technology we acquired through our acquisition of Guide; conduct research activities as we seek to discover and develop additional product candidates; maintain, expand, enforce, defend and protect our intellectual property portfolio; and continue to hire research and development, clinical, technical operations and commercial personnel. In addition, we expect to continue to incur the costs associated with operating as a public company.

As a result of these anticipated expenditures, we will need to raise additional capital to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, strategic alliances, and licensing arrangements. We may be unable to raise additional funds or enter into such other agreements when needed on favorable terms or at all. Our inability 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 can give no assurance that we will be able to secure such additional sources of capital to support our operations, or, if such capital is available to us, that such additional capital will be sufficient to meet our needs for the short or long term.

## **Revenue Recognition**

In April 2019, we entered into a collaboration and license agreement, or the Verve Agreement, with Verve Therapeutics, Inc., or Verve, a company focused on gene editing for cardiovascular disease treatments. In June 2021, we entered into a research collaboration agreement, or the Apellis Agreement, with Apellis Pharmaceuticals, Inc., or Apellis, focused on the use of certain of our base editing technology to discover new treatments for complement system-driven diseases. In October 2021, we entered into an option and license agreement, or the Sana Agreement, with Sana Biotechnology, Inc., or Sana, pursuant to which we granted Sana non-exclusive research and development and commercial rights to our CRISPR Cas12b technology to perform nuclease editing for certain *ex vivo* engineered cell therapy programs. In December 2021, we entered into a four-year research collaboration agreement, or the Pfizer Agreement, with Pfizer Inc., or Pfizer, focused on *in vivo* base editing programs for three targets for rare genetic diseases of the liver, muscle and central nervous system.

We have not generated any revenue to date from product sales and do not expect to do so in the near future. During the years ended December 31, 2021, 2020, and 2019, we recognized \$51.8 million, \$24,000 and \$18,000, respectively, of revenue. In 2021, our revenue recorded was related to our collaboration and license agreements with Sana, Apellis and Verve. In 2020 and 2019, our revenue recorded was related to our license agreement with Verve.

For additional information about our revenue recognition policy, see Note 2 and Note 10 of the notes to our audited consolidated financial statements included in this Annual Report on Form 10-K.

## **Research and development expenses**

Research and development expenses consist of costs incurred in performing research and development activities, which include:

- Expenses incurred in connection with investments in delivery technology for our base editors, including the LNP technology we acquired through our acquisition of Guide;
- the cost to obtain licenses to intellectual property, such as those with Harvard University, or Harvard, The Broad Institute, Inc., or Broad Institute, Editas Medicine, Inc, or Editas, and Bio Palette Co., Ltd., or Bio Palette, and related future payments should certain success, development and regulatory milestones be achieved;
- personnel-related expenses, including salaries, bonuses, benefits and stock-based compensation for employees engaged in research and development functions;
- expenses incurred in connection with the discovery and preclinical development of our research programs, including under agreements with third parties, such as consultants, contractors and contract research organizations;
- expenses incurred in connection with the initiation of clinical trials, including CRO costs and costs related to study preparation;
- expenses incurred in connection with regulatory filings;
- expenses incurred in connection with the building of our base editing platform;
- the cost of manufacturing for use in our preclinical studies, IND-enabling studies and clinical trials;
- laboratory supplies and research materials; and
- facilities, depreciation and other expenses which include direct and allocated expenses.

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 benefits are consumed.

In the early phases of development, our research and development costs are often devoted to product platform and proof-of-concept preclinical studies that are not necessarily allocable to a specific target.

We expect that our research and development expenses will increase substantially as we advance our programs through their planned preclinical and clinical development.

## **General and administrative expenses**

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in our executive, intellectual property, business development and administrative functions. General and administrative expenses also include legal fees relating to intellectual property and corporate matters, professional fees for accounting, auditing, tax and consulting services, insurance costs, travel, and direct and allocated facility related expenses and other operating costs.

We anticipate that our general and administrative expenses will increase in the future to support our increased research and development activities. We also expect to continue to incur costs associated with being a public company and maintaining controls over financial reporting, including costs of accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with Nasdaq and SEC requirements, director and officer insurance costs, and investor and public relations costs.

#### Other income and expenses

Other income and expenses consist of the following items:

- *Change in fair value of derivative liabilities* consists primarily of remeasurement gains or losses associated with changes in success payment liabilities associated with our license agreement with Harvard, dated as of June 27, 2017, as amended, or the Harvard License Agreement, and the license agreement with The Broad Institute, as amended, dated as of May 9, 2018, or the Broad License Agreement.
- *Change in fair value of non-controlling equity investments* consists of mark-to-market adjustments related to our investments in equity securities.
- *Change in fair value of contingent consideration liabilities* consists of remeasurement of the fair market value of the technology and product contingent consideration liabilities related to the acquisition of Guide.
- *Interest and other income (expense), net* consists primarily of interest income as well as interest expense related to our equipment financings.

#### Results of operations

##### Comparison of the years ended December 31, 2021 and 2020

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

	Years Ended December 31,		Change
	2021	2020	
License and collaboration revenue	\$ 51,844	\$ 24	\$ 51,820
Operating expenses:			
Research and development	387,087	103,179	283,908
General and administrative	57,222	29,605	27,617
Total operating expenses	444,309	132,784	311,525
Loss from operations	(392,465)	(132,760)	(259,705)
Other income (expense):			
Change in fair value of derivative liabilities	(1,000)	(63,400)	62,400
Change in fair value of non-controlling equity investments	17,690	517	17,173
Change in fair value of contingent consideration liabilities	5,146	—	5,146
Interest and other income (expense), net	(9)	1,051	(1,060)
Total other income (expense)	21,827	(61,832)	83,659
Net loss	\$ (370,638)	\$ (194,592)	\$ (176,046)

##### License and collaboration revenue

License and collaboration revenue was approximately \$51.8 million for the year ended December 31, 2021 compared to approximately \$24,000 for the year ended December 31, 2020. License and collaboration revenue recorded in 2021 represents revenue recorded under the Sana, Apellis and Verve Agreements. We recorded \$50.0 million of license revenue related to the Sana Agreement for the twelve months ended December 31, 2021. License and collaboration revenue recorded in 2020 represents revenue recorded under the Verve Agreement.

##### Research and development expenses

Research and development expenses were \$387.1 million and \$103.2 million for the years ended December 31, 2021 and 2020, respectively. The increase of \$283.9 million was primarily due to the following:

- \$155.0 million of expense related to in-process research and development asset acquired from Guide as there was determined to be no alternative future use.
- An increase of \$32.7 million in milestone and license expenses. During the year ended December 31, 2021, we recorded \$39.9 million in non-royalty sublicense fees and \$0.9 million of expense for milestones related to our technology license agreements. During the year ended December 31, 2020, we recognized \$5.5 million in expense representing the fair value of the common stock we issued to Prime Medicine Inc., or Prime Medicine, in October 2020 and \$2.3 million expense for a milestone payment made to Bio Palette, upon the issuance of a certain patent in the United States becoming probable.

- Increases of \$22.9 million in personnel-related costs and \$15.4 million in facility-related costs, including depreciation. These increases were due to the growth in the number of research and development employees from 149 at December 31, 2020 to 279 at December 31, 2021, and their related activities, as well as the expense allocated to research and development related to our leased facilities.
- An increase of \$21.2 million in outsourced services, driven by process development, IND-enabling materials and clinical readiness spend for BEAM-101, BEAM-201 and BEAM-102, assay development and qualification of gRNA and mRNA materials for BEAM-101 and BEAM-201, and toxicology studies and activities for BEAM-101, BEAM-102 and BEAM-201.
- An increase of \$15.5 million in stock-based compensation from additional stock options and restricted stock units granted due to the increase in the number of research and development employees, additional grants given to existing employees, as well as an increase in the value of our common stock.
- An increase of \$15.1 million in lab supplies due to the movement of our lead programs into IND-enabling activities and continued investment in platform and discovery efforts.
- An increase of \$6.1 million in other expenses, primarily related to an increase in research and development specific software costs.

Research and development expenses are expected to continue to increase as we initiate clinical trials for BEAM-101, continue IND-enabling studies for BEAM-102 and BEAM-201, begin IND-enabling studies for BEAM-301, continue our current research programs, initiate new research programs, continue the preclinical and clinical development of our product candidates and conduct any future preclinical studies and begin to enroll patients in and conduct clinical trials for any of our product candidates.

#### *General and administrative expenses*

General and administrative expenses were \$57.2 million and \$29.6 million for the years ended December 31, 2021 and 2020, respectively. The increase of \$27.6 million was primarily due to the following:

- An increase of \$12.8 million in stock-based compensation from additional stock options and restricted stock units granted due to an increase in the number of general and administrative employees from 32 employees as of December 31, 2020 to 62 employees as of December 31, 2021, additional grants given to existing employees, as well as an increase in the value of our common stock.
- Increases of \$9.3 million in personnel related costs and \$1.3 million in facility related costs, including depreciation costs, due to the increase in the number of general and administrative employees, as well as the expense allocated to general and administrative expenses related to our leased facilities.
- An increase of \$3.2 million in legal costs primarily due to legal fees incurred in connection with our acquisition of Guide, as well as the completion of the Apellis, Sana and Pfizer Agreements.
- An increase of \$1.6 million in insurance costs due to increased directors and officers insurance costs as a result of our IPO in February 2020 and insurance costs related to our acquisition of Guide in 2021.

#### *Change in fair value of derivative liabilities*

During the year ended December 31, 2021, we recorded a \$1.0 million expense related to the change in fair value expense related to the success payment liabilities as compared to a \$63.4 million expense for the year ended December 31, 2020. We did not experience a significant change in our closing stock price at the end of 2021, as compared to the closing stock price at the end of 2020. A portion of the success payments was paid in June 2021; the remaining success payment obligations are still outstanding as of December 31, 2021 and will continue to be revalued at each reporting period.

#### *Change in fair value of non-controlling equity investments*

During the years ended December 31, 2021 and December 31, 2020, we recorded other income of \$17.7 million and \$0.5 million, respectively, as a result of increases in the value of our investment in Verve's common stock.

#### *Change in contingent consideration liabilities*

During the year ended December 31, 2021, we recorded \$5.1 million of other income related to the change in fair value of the Guide technology and product contingent consideration liabilities as a result of an update in project timelines and the expected probability of achievement of the milestones.

### *Interest and other income (expense), net*

Interest and other income (expense), net was \$9,000 for the year ended December 31, 2021 as compared to \$1.1 million of income for the year ended December 31, 2020. The decrease was primarily due to interest expense on our equipment financing, which was greater than interest income driven by a decrease in interest rates earned on our investments.

### **Comparison of the years ended December 31, 2020 and 2019**

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

	Years Ended December 31,		Change
	2020	2019	
License revenue	\$ 24	\$ 18	\$ 6
Operating expenses:			
Research and development	\$ 103,179	\$ 54,619	\$ 48,560
General and administrative	29,605	20,553	9,052
Total operating expenses	132,784	75,172	57,612
Loss from operations	(132,760)	(75,154)	(57,606)
Other income (expense):			
Change in fair value of derivative liabilities	(63,400)	(5,400)	(58,000)
Change in fair value of non-controlling equity investments	517	—	517
Interest and other income (expense), net	1,051	2,228	(1,177)
Total other income (expense)	(61,832)	(3,172)	(58,660)
Net loss	\$ (194,592)	\$ (78,326)	\$ (116,266)

### *License revenue*

License revenue was approximately \$24,000 for the year ended December 31, 2020 compared to approximately \$18,000 for the year ended December 31, 2019. License revenue represents Verve license revenue recorded under the Collaboration and License Agreement executed in April 2019.

### *Research and development expenses*

Research and development expenses were \$103.2 million and \$54.6 million for the years ended December 31, 2020 and 2019, respectively. The increase of \$48.6 million was primarily due to the following:

- An increase of \$20.8 million in outsourced services and lab supplies, driven primarily by external research services such as CMOs, IND-enabling studies and sponsored research agreements.
- An increase of \$5.9 million in milestone and license expenses, primarily related to our agreement with Prime Medicine. During the year ended December 31, 2020, we recognized \$5.5 million of expense, representing the fair value of our common stock issued to Prime Medicine in October 2020.
- Increases of \$8.6 million in personnel-related costs and \$5.6 million in facility-related costs, including depreciation. These increases were due to the growth in the number of research and development employees from 97 at December 31, 2019 to 149 at December 31, 2020, and their related activities, as well as the expense allocated to research and development related to our leased facilities.
- An increase of \$7.0 million in stock-based compensation from additional stock options and restricted stock awards granted due to the increase in the number of research and development employees, as well as an increase in the value of our common stock.

Research and development expenses will continue to increase as we continue our current research programs, initiate new research programs, continue our preclinical development of product candidates and conduct future clinical trials for any of our product candidates.

### *General and administrative expenses*

General and administrative expenses were \$29.6 million and \$20.6 million for the years ended December 31, 2020 and 2019, respectively. The increase of \$9.1 million was primarily due to the following:

- An increase of \$2.9 million in insurance costs due to increased directors and officers insurance costs as a result of our being a public company.
- Increases of \$2.7 million in personnel related costs and \$1.1 million in other (primarily information technology related) costs due to an increase in general and administrative employees from 21 employees as of December 31, 2019 to 32 employees as of December 31, 2020.

- An increase of \$1.5 million in intellectual property costs, offset by a \$0.6 million decrease in corporate legal expenses.
- An increase of \$1.4 million in stock-based compensation from additional stock options granted due to an increase in the number of general and administrative employees, as well as an increase in the value of our common stock.

#### *Change in fair value of derivative liabilities*

During the year ended December 31, 2020, we recorded a \$63.4 million change in fair value expense related to the success payment liabilities as compared to a \$5.4 million expense for the year ended December 31, 2019, due to a significant increase in the value of our common stock.

#### *Change in fair value of non-controlling equity investments*

During the year ended December 31, 2020, we recorded other income of \$0.5 million as a result of an increase in the value of our investment in Verve's common stock.

#### *Interest and other income (expense), net*

Interest and other income (expense), net was \$1.1 million for the year ended December 31, 2020 as compared to \$2.2 million for the year ended December 31, 2019. The decrease of \$1.2 million was primarily due to a decrease in interest income of \$1.1 million as a result of decreases in interest rates related to our investment portfolio and an increase in interest expense of \$0.4 million due to the occurrence of additional drawdowns on our equipment line in 2020.

#### **Liquidity and capital resources**

Since our inception in January 2017, we have not generated any revenue from product sales, have generated only limited license and collaboration revenue from the Verve Agreement, the Apellis Agreement and the Sana Agreement, and have incurred significant operating losses and negative cash flows from our operations. We expect to incur significant expenses and operating losses for the foreseeable future as we advance the preclinical and the clinical development of our product candidates.

To date, we have funded our operations primarily through equity offerings. In February 2020, we completed our IPO in which we issued and sold 12,176,471 shares of our common stock, including 1,588,235 shares of common stock sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a public offering price of \$17.00 per share. We received net proceeds from our IPO of \$188.3 million, after deducting underwriting discounts and offering expenses payable by us. In October 2020, we issued and sold 5,750,000 shares of our common stock, including 750,000 shares pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of \$23.50 per share, for aggregate gross proceeds of \$135.1 million. We received approximately \$126.6 million in net proceeds after deducting applicable underwriting discounts and offering expenses. In January 2021, we issued and sold 2,795,700 shares of our common stock in a private placement at an offering price of \$93.00 per share for aggregate gross proceeds of \$260.0 million. We received \$252.0 million in net proceeds after deducting offering expenses payable by us.

In April 2021, we filed a universal automatic shelf registration statement on Form S-3 with the SEC, or the 2021 Shelf, to register for sale an indeterminate amount of our common stock, preferred stock, debt securities, warrants and/or units in one or more offerings, which became effective upon filing with the SEC (File No. 333-254946).

In April 2021, we entered into an at the market, or ATM, sales agreement, or the Sales Agreement, with Jefferies LLC, or Jefferies, pursuant to which we were entitled to offer and sell, from time to time at prevailing market prices, shares of our common stock having aggregate gross proceeds of up to \$300.0 million. We agreed to pay Jefferies a commission of up to 3.0% of the aggregate gross sale proceeds of any shares sold by Jefferies under the Sales Agreement. As of December 31, 2021, we have sold 2,908,009 shares of our common stock under the Sales Agreement at an average price of \$103.16 per share for aggregate gross proceeds of \$300.0 million, before deducting commissions and offering expenses payable by us.

In July 2021, we and Jefferies entered into an amendment to the Sales Agreement to provide for an increase in the aggregate offering amount under the Sales Agreement, such that as of July 7, 2021, we may offer and sell shares of common stock having an aggregate offering price of an additional \$500.0 million. As of December 31, 2021, we have sold 1,999,186 additional shares of our common stock under the amended Sales Agreement at an average price of \$105.65 per share for aggregate gross proceeds of \$211.2 million, before deducting commissions and offering expenses payable by us, resulting in an aggregate of \$511.2 million in gross proceeds received under the Sales Agreement as of December 31, 2021.

In June 2021, we entered into the Apellis Agreement, which is focused on the use of certain of our base editing technology to discover new treatments for complement system-driven diseases. Pursuant to the Apellis Agreement, we received an upfront payment of \$50.0 million in July 2021. We are also eligible to receive an additional payment of \$25.0 million on June 30, 2022, the one-year anniversary of the effective date of the Apellis Agreement.



In October 2021, we entered into the Sana Agreement, pursuant to which we granted Sana non-exclusive research and development commercial rights to our CRISPR Cas12b technology to perform nuclease editing for certain *ex vivo* engineered cell therapy programs. Pursuant to the Sana Agreement, we received an upfront payment of \$50.0 million in October 2021.

In December 2021, we entered into the Pfizer Agreement, which is focused on *in vivo* base editing programs for three targets for rare genetic diseases of the liver, muscle and central nervous system. Under the terms of the Pfizer Agreement, we will conduct all research activities through development candidate selection for three undisclosed targets, which are not included in our existing programs. Pursuant to the Pfizer Agreement, we received an upfront payment of \$300.0 million in January 2022. As we did not receive the \$300.0 million upfront fee before December 31, 2021, we recorded a collaboration receivable for \$300.0 million with a corresponding deferred revenue liability in our consolidated financial statements for the year ended December 31, 2021

As of December 31, 2021, we had \$965.6 million in cash, cash equivalents, and marketable securities.

We are required to make success payments to Harvard and Broad Institute based on increases in the per share fair market value of our Series A-1 Preferred Stock and Series A-2 Preferred Stock or, subsequent to our IPO, our common stock. The amounts due may be settled in cash or shares of our common stock, at our discretion. In May 2021, the first success payment measurements occurred and success payments to Harvard and Broad Institute were calculated to be \$15.0 million and \$15.0 million, respectively. We elected to make each payment in shares of our common stock and issued 174,825 shares to each of Harvard and Broad Institute to settle these liabilities in June 2021. We may additionally owe Harvard and Broad Institute success payments of up to an additional \$90.0 million each.

We have not yet commercialized any of our product candidates, and we do not expect to generate revenue from the sale of our product candidates for the foreseeable future. We anticipate that we may need to raise additional capital in order to continue to fund our research and development, including our planned preclinical studies and clinical trials, building, maintaining and operating a commercial-scale cGMP manufacturing facility, and new product development, as well as to fund our general operations. As necessary, we will seek to raise additional capital through various potential sources, such as equity and debt financings or through corporate collaboration and license agreements. We can give no assurances that we will be able to secure such additional sources of capital to support our operations, or, if such funds are available to us, that such additional financing will be sufficient to meet our needs.

### Cash flows

The following table summarizes our sources and uses of cash (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Net cash used in operating activities	\$ (66,268)	\$ (95,741)	\$ (72,003)
Net cash used in investing activities	(294,144)	(100,123)	(66,659)
Net cash provided by financing activities	756,141	322,322	41,279
Net increase (decrease) in cash, cash equivalents and restricted cash	\$ 395,729	\$ 126,458	\$ (97,383)

### Operating activities

Net cash used in operating activities for the year ended December 31, 2021 was \$66.3 million, consisting primarily of our net loss of \$370.6 million and an increase in collaboration receivable of \$300.0 million, primarily related to the Pfizer Agreement, as well as noncash items including an increase in the fair value of a non-controlling equity investment of \$17.7 million and a change in the fair value of contingent consideration liabilities of \$5.1 million. These uses of cash were offset in part by cash provided by increases in deferred revenue of \$348.2 million, primarily related to the Pfizer and Apellis Agreements, other accrued expenses and other liabilities of \$43.9 million, operating lease liabilities of \$16.0 million and accounts payable and other long-term liabilities of \$2.6 million as well as noncash items consisting primarily of in-process research and development of \$155.0 million, stock-based compensation expense of \$43.6 million, change in operating lease ROU assets of \$9.0 million, depreciation and amortization expense of \$7.5 million and change in fair value of derivative liabilities of \$1.0 million.

Net cash used in operating activities for the year ended December 31, 2020 was \$95.7 million, consisting primarily of our net loss of \$194.6 million and an increase in prepaid expenses and other current assets of \$5.7 million, offset by cash provided by increases in accrued expenses of \$7.0 million, operating lease liabilities of \$3.2 million and long-term liabilities of \$1.0 million. Net cash used in operating activities was also offset by non-cash charges consisting primarily of a change in the fair value of derivative liabilities of \$63.4 million, stock-based compensation expense of \$15.4 million, non-cash license expenses of \$5.7 million, depreciation of \$4.7 million, and non-cash lease expense of \$4.7 million, offset by a \$0.5 million non-cash change in the fair value of equity investments.

Net cash used in operating activities for the year ended December 31, 2019 was \$72.0 million, consisting primarily of our net loss of \$78.3 million, a decrease in financing milestone liabilities of \$13.8 million resulting from payment of these liabilities, a decrease in operating lease liabilities of \$2.5 million, and an increase in prepaids and other assets of \$1.9 million offset by cash provided by increases in accounts payable and accrued expenses of \$7.7 million and non-cash charges consisting primarily of stock based compensation expense of \$7.0 million, change in fair value of derivative liabilities of \$5.4 million, depreciation of \$3.5 million, and non-cash lease expense of \$1.9 million, offset by amortization of investment premiums of \$0.9 million.

#### *Investing activities*

For the year ended December 31, 2021, cash used in investing activities was primarily the net result of purchases of marketable securities partially offset by maturities of marketable securities of \$248.0 million, in addition to purchases of property and equipment of \$46.8 million. We also received \$0.6 million in net cash from our acquisition of Guide, after the payment of acquisition costs.

For the year ended December 31, 2020, cash used in investing activities was primarily the net result of purchases of marketable securities partially offset by maturities of marketable securities of \$83.0 million, in addition to purchases of property and equipment of \$16.4 million.

For the year ended December 31, 2019, cash used in investing activities was primarily the net result of purchases of marketable securities partially offset by maturities of marketable securities of \$53.7 million, in addition to purchases of property and equipment of \$12.5 million.

#### *Financing activities*

Net cash provided by financing activities for the year ended December 31, 2021 consisted primarily of proceeds from equity offerings of \$757.4 million and proceeds from the exercise of stock options of \$9.6 million, offset in part by the payment of equity offering costs of \$8.8 million and repayments of equipment financing liabilities of \$2.1 million.

Net cash provided by financing activities for the year ended December 31, 2020 consisted primarily of proceeds from our IPO and follow-on public offering of \$319.5 million, net of underwriting discounts, net proceeds of \$3.3 million from equipment financing, and proceeds from the exercise of stock options of \$3.2 million, offset in part by the payment of equity offering costs of \$2.1 million and repayments of equipment financing liabilities of \$1.6 million.

Net cash provided by financing activities for the year ended December 31, 2019 consisted primarily of the net proceeds from the issuance of Series B Preferred Stock of \$37.9 million, and net proceeds of \$5.7 million from equipment financing, offset by the payment of equity issuance costs of \$2.5 million.

#### *Funding requirements*

Our operating expenses are expected to increase substantially as we continue to advance our portfolio of programs.

Specifically, our expenses will increase if and as we:

- initiate clinical trials of our product candidates, including our BEACON-101 trial;
- continue our research programs and our preclinical development of product candidates from our research programs;
- seek to identify additional research programs and additional product candidates;
- initiate preclinical studies and clinical trials for additional product candidates we identify and develop;
- maintain, expand, enforce, defend, and protect our intellectual property portfolio and provide reimbursement of third-party expenses related to our patent portfolio;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- establish a sales, marketing, and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;
- further develop our base editing platform;
- further develop delivery technology for our base editors, including the LNP technology we acquired through our acquisition of Guide;
- continue to hire additional personnel including research and development, clinical and commercial personnel;
- add operational, financial, and management information systems and personnel, including personnel to support our product development;

- acquire or in-license products, intellectual property, medicines and technologies; and
- build, maintain, and operate a commercial-scale cGMP manufacturing facility.

We expect that our cash, cash equivalents at December 31, 2021 will enable us to fund our current and planned operating expenses and capital expenditures for at least the twelve calendar months beginning January 1, 2022 and beyond such twelve-month period. We have based these estimates on assumptions that may prove to be imprecise, and we may exhaust our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development of our programs, we are unable to estimate the amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates.

Our future funding requirements will depend on many factors including:

- the cost of continuing to build our base editing platform;
- the costs of acquiring licenses for the delivery modalities that will be used with our product candidates;
- the scope, progress, results, and costs of discovery, preclinical development, laboratory testing, manufacturing and clinical trials for the product candidates we may develop;
- the costs of preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property and proprietary rights, and defending intellectual property-related claims;
- the costs, timing, and outcome of regulatory review of the product candidates we develop;
- the costs of future activities, including product sales, medical affairs, marketing, manufacturing, distribution, coverage and reimbursement for any product candidates for which we receive regulatory approval;
- the success of our license agreements and our collaborations;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any collaboration agreements we are a party to or may become a party to;
- the payment of success liabilities to Harvard and Broad Institute pursuant to the respective terms of the Harvard License Agreement and the Broad Institute License Agreement, should we choose to pay in cash;
- the extent to which we acquire or in-license products, intellectual property, and technologies;
- the costs of obtaining, building, operating and expanding our manufacturing capacity; and
- the impacts of the COVID-19 pandemic and our response to it.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. Further, our operating plans may change in the future, and we may need additional funds to meet operational needs and capital requirements associated with such operating plans.

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 licensing arrangements. We do not have any committed external source of capital. We have historically relied on equity issuances to fund our capital needs and will likely rely on equity issuances in the future. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures, or declaring dividends.

If we raise capital through additional 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 we may have to grant licenses on terms that may not be favorable to us. If we are unable to raise additional capital through equity or debt financings when needed, we may be required to delay, limit, reduce, or terminate our product development or, if approved, future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. We can give no assurance that we will be able to secure such additional sources of funds to support our operations, or, if such funds are available to us, that such additional funding will be sufficient to meet our needs.

## **Contractual obligations**

We lease certain assets under noncancelable operating and finance leases, which expire through 2034. The leases relate primarily to office space and laboratory space in addition to equipment. Aggregate future minimum commitments under these office and laboratory leases and equipment leases are \$204.6 million and \$5.2 million, respectively, as of December 31, 2021, excluding any related common area maintenance charges or real estate taxes.

In August 2021, we executed a lease amendment to our April 2019 lease for office and laboratory space in Cambridge, Massachusetts to occupy additional space. The term of this lease will run concurrent with the term of the April 2019 lease. The initial estimate of the minimum amount of undiscounted lease payments due under this lease is \$11.1 million which is not included in the aggregate future minimum lease commitments amounts discussed above.

In addition, the aggregate future minimum lease commitments amounts discussed above do not include our lease agreement with Alexandria Real Estate Equities, Inc. to build a 100,000 square foot manufacturing facility in Research Triangle Park, North Carolina. The initial estimate of minimum amount of undiscounted lease payments due under this lease is \$69.0 million, which is expected to be paid over a lease term of 15 years.

In May 2021, the first success payment measurements under the Harvard License Agreement and Broad License Agreement occurred and success payments to Harvard and Broad Institute were calculated to be \$15.0 million and \$15.0 million, respectively. We elected to make each payment in shares of our common stock and issued 174,825 shares of our common stock to each of Harvard and Broad Institute to settle these liabilities in June 2021. The remaining success payment obligations are still outstanding as of December 31, 2021. We may additionally owe Harvard and Broad Institute success payments of up to an additional \$90.0 million each.

The aggregate future minimum commitments amounts discussed above also do not include potential milestone and success fees, non-royalty sublicense income fees, royalty fees, licensing maintenance fees, and reimbursement of patent maintenance costs that we may be required to pay under agreements we have entered into with certain institutions to license intellectual property. Our agreements to license intellectual property include potential milestone payments that are dependent upon the development of products using the intellectual property licensed under the agreements and contingent upon the achievement of development or regulatory approval milestones, as well as commercial and success payment milestones. We have not included such amounts in the aggregate future minimum commitments amounts discussed above because they are contingent upon the occurrence of future events and the timing and likelihood of such potential obligations are not known with certainty.

In addition, we agreed to pay Guide's former stockholders and optionholders up to an additional \$100.0 million in technology milestone payments and \$220.0 million in product milestone payments, payable in our common stock valued using the volume-weighted average price of our common stock over the ten-day trading period ending two trading days prior to the date on which the applicable milestone is received. The amounts discussed above do not include such payments because they are contingent upon the occurrence of future events and the timing and likelihood of such potential obligations are not known with certainty.

Additionally, we enter into contracts in the normal course of business with CROs, CMOs and other vendors to assist in the performance of our research and development activities and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancelable contracts and not included in the aggregate future minimum commitments amounts discussed above.

## **Critical accounting policies and significant judgements and estimates**

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

While our significant accounting policies are described in more detail in Note 2, *Summary of significant accounting policies*, to our consolidated financial statements in this Annual Report on Form 10-K, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our financial statements.

### **Revenue recognition**

We recognize revenue in accordance with ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* and its related amendments, or, collectively, ASC 606.

At inception, we determine whether contracts are within the scope of ASC 606 or other topics. For contracts that are determined to be within the scope of ASC 606, revenue is recognized when a customer obtains control of promised goods or services. The amount of revenue recognized reflects the consideration to which we expect to be entitled to receive in exchange for these goods and services. To achieve this core principle, we apply the following five steps (i) identify the contract with the customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when the performance obligation is satisfied. We only apply the five-step model to contracts when we determine that collection of substantially all consideration for goods and services that are transferred is probable based on the customer's intent and ability to pay the promised consideration.

Performance obligations promised in a contract are identified based on the goods and services that will be transferred to the customer that are both capable of being distinct and are distinct in the context of the contract. To the extent a contract includes multiple promised goods and services, we apply judgment to determine whether promised goods and services are both capable of being distinct and are distinct in the context of the contract. If these criteria are not met, the promised goods and services are accounted for as a combined performance obligation.

The transaction price is determined based on the consideration to which we will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration, we estimate the amount of variable consideration that should be included in the transaction price utilizing either the expected value method or the most likely amount method, depending on the nature of the variable consideration. Variable consideration is included in the transaction price if, in management's judgment, it is probable that a significant future reversal of cumulative revenue under the contract will not occur. Any estimates, including the effect of the constraint on variable consideration, are evaluated at each reporting period for any changes. Determining the transaction price requires significant judgment and is discussed in further detail for each of our license and collaboration agreements in Note 10, *Collaboration and license agreements*, to our consolidated financial statements in this Annual Report on Form 10-K, or Note 10.

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price to each performance obligation on a relative standalone selling price basis unless the transaction price is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct service that forms part of a single performance obligation. The consideration to be received is allocated among the separate performance obligations based on relative standalone selling prices. Determining the standalone selling price requires significant judgment and is discussed in further detail for each of our license and collaboration agreements in Note 10.

We satisfy performance obligations either over time or at a point in time. Revenue is recognized over time if either (i) the customer simultaneously receives and consumes the benefits provided by the entity's performance, (ii) the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or (iii) the entity's performance does not create an asset with an alternative use to the entity and the entity has an enforceable right to payment for performance completed to date. If the entity does not satisfy a performance obligation over time, the related performance obligation is satisfied at a point in time by transferring the control of a promised good or service to a customer.

The timing of when services are performed and the occurrence of external costs associated with the programs under the collaboration agreements could impact how revenue is recognized in a certain period.

Licenses of intellectual property, or IP: If the license to our IP is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from consideration allocated to the license when the license is transferred to the customer and the customer can use and benefit from the licenses. For licenses that are combined with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition. Determining the revenue recognition of IP licenses requires significant judgment and is discussed in further detail for each of our license and collaboration agreements in Note 10.

Milestone payments: At the inception of each arrangement that includes development or regulatory milestone payments, we evaluate the probability of reaching the milestones and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur in the future, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee's, such as regulatory approvals, are not considered probable of being achieved until those approvals are received and therefore revenue recognized is constrained as management is unable to assert that a reversal of revenue would not be possible. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such development milestones and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment. To date, we have not recognized any milestone revenue resulting from any of our agreements.

Commercial Milestone Payments and Royalties: For arrangements that include sales-based royalties, including milestone payments based on levels of sales, if the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, we have not recognized any royalty revenue resulting from any of our agreements.

When no performance obligations are required of us, or following the completion of the performance obligation period, such amounts are recognized as revenue upon transfer of control of the goods or services to the customer. Generally, all amounts received or due other than sales-based milestones and royalties are classified as license and collaboration revenue. Sales-based milestones and royalties will be recognized as royalty revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Deferred revenue expected to be recognized within the next twelve months is classified as a current liability.

#### **Asset Acquisitions**

In 2018, we adopted ASU 2017-01, *Business Combinations*, or ASU 2017-01, which clarified the definition of a business. We measure and recognize asset acquisitions that are not deemed to be business combinations based on the cost to acquire the assets, which includes transaction costs, and the consideration is allocated to the items acquired based on a relative fair value methodology. Goodwill is not recognized in asset acquisitions. In an asset acquisition, the cost allocated to acquire in-process research and development with no alternative future use is charged to research and development expense at the acquisition date.

At the time of acquisition, we determine if a transaction should be accounted for as a business combination or acquisition of assets.

#### **Contingent Consideration Liabilities**

We may be required to make milestone payments to the former stockholders and optionholders of Guide in the form of our common stock based on the achievement of certain product and technology milestones. The payments are accounted for under ASC 480, *Distinguishing Liabilities from Equity*. These contingent consideration liabilities are carried at fair value which was estimated by applying a probability-based model, which utilized inputs primarily based upon the achievement and related timing of certain product and technology milestones that were unobservable in the market. The estimated fair value of contingent consideration liabilities, initially measured and recorded on the acquisition date, are considered to be a Level 3 measurement and are reviewed quarterly, or whenever events or circumstances occur that indicate a change in fair value. The contingent consideration liabilities are recorded at fair value at the end of each reporting period with changes in estimated fair values recorded in other income (expense) in the consolidated statements of operations and other comprehensive loss.

The estimated fair value is determined based on probability adjusted discounted cash flow models that include significant estimates and assumptions pertaining to technology and product development. Significant changes in any of the probabilities of success would result in a significantly higher or lower fair value measurement. Significant changes in the probabilities as to the periods in which milestones will be achieved would result in a significantly lower or higher fair value measurement.

#### **Fair value measurements – Success payments**

We are required to make success payments to Harvard and Broad Institute based on increases in the per share fair market value of our Series A-1 Preferred Stock and Series A-2 Preferred Stock or, subsequent to our IPO, our common stock. Any amounts due may be settled in cash or shares of our common stock, at our discretion. The success payments are accounted for under Accounting Standards Codification 815, *Derivatives and Hedging* and were initially recorded at fair value with a corresponding charge to research and development expense. The liabilities are marked to market at each balance sheet date with all changes in value recognized in interest and other income (expense) in the consolidated statement of operations and other comprehensive loss. We will continue to adjust the liability for changes in fair value until the earlier of the achievement or expiration of the success payment obligation. To determine the estimated fair value of the success payments, we used a Monte Carlo simulation model, which models the value of the liability based on several key variables, including probability of event occurrence, timing of event occurrence, as well as the price per share at the time of success payment. A significant change in our stock price or volatility could have a significant impact on the value of the liability.

#### **Accrued research and development costs**

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to vendors in connection with preclinical development activities and vendors related to development, manufacturing and distribution of product candidate materials.

We base our expenses related to preclinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple vendors that conduct and manage preclinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. 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 and adjust accordingly.

### **Stock-based compensation**

We measure stock options and other stock-based awards granted to our employees, directors, consultants or founders based upon their fair value on the date of the grant and recognize stock-based compensation expense over the requisite service period, which is generally the vesting period of the respective award. We recognize forfeitures as they occur.

The majority of our stock-based compensation awards are subject to service-based vesting conditions. We apply the straight-line method of expense recognition to all awards with service-based vesting. We also have performance-based awards, where stock-based compensation expense is recognized over the service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

We estimate the fair value of each stock option grant on the date of grant using the Black-Scholes option-pricing model, which uses inputs such as the fair value of our common stock, assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. The fair value of our common stock is used to determine the fair value of restricted stock awards.

Prior to our IPO in February 2020, there was no public market for our common stock. As a result, prior to our IPO, the estimated fair value of our common stock was determined by our board of directors as of the date of each option grant, with input from management, considering our most recently available third-party valuations of common stock and our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent valuation through the date of the grant. Following our IPO, the fair value of our common stock is determined based on the quoted market price of our common stock.

### **Leases**

On January 1, 2019, we adopted ASU No. 2016-02, *Leases (Topic 842)*, or ASC 842, which requires the recognition of the right-of-use assets and related operating and finance lease liabilities on the balance sheet.

For contracts entered into on or after the effective date, at the inception of a contract, we assess whether the contract is, or contains, a lease. The assessment is based on: (1) whether the contract involves the use of a distinct identified asset, (2) whether we obtain the right to substantially all the economic benefit from the use of the asset throughout the period, and (3) whether we have the right to direct the use of the asset. At inception of a lease, we allocate the consideration in the contract to each lease component based on its relative stand-alone price to determine the lease payments.

Leases are classified as either finance leases or operating leases. A lease is classified as a finance lease if any one of the following criteria are met: the lease transfers ownership of the asset by the end of the lease term, the lease contains an option to purchase the asset that is reasonably certain to be exercised, the lease term is for a major part of the remaining useful life of the asset or the present value of the lease payments equals or exceeds substantially all of the fair value of the asset. A lease is classified as an operating lease if it does not meet any of these criteria.

For all leases at the lease commencement date, a right-of-use asset and a lease liability are recognized. The right-of-use asset represents the right to use the leased asset for the lease term. The lease liability represents the present value of the lease payments under the lease.

The right-of-use asset is initially measured at cost, which primarily comprises the initial amount of the lease liability, plus any initial direct costs incurred if any, less any lease incentives received. All right-of-use assets are reviewed for impairment. The lease liability is initially measured at the present value of the lease payments, discounted using the interest rate implicit in the lease or, if that rate cannot be readily determined, our secured incremental borrowing rate for the same term as the underlying lease. For real estate leases and other operating leases, we use our secured incremental borrowing rate. For finance leases, we use the rate implicit in the lease or our secured incremental borrowing rate if the implicit lease rate cannot be determined.

Lease payments included in the measurement of the lease liability comprise the following: the fixed noncancelable lease payments, payments for optional renewal periods where it is reasonably certain the renewal period will be exercised, and payments for early termination options unless it is reasonably certain the lease will not be terminated early.

Lease cost for operating leases consists of the lease payments plus any initial direct costs, primarily brokerage commissions, and is recognized on a straight-line basis over the lease term. Included in lease cost are any variable lease payments incurred in the period that are not included in the initial lease liability and lease payments incurred in the period for any leases with an initial term of 12 months or less. Lease cost for finance leases consists of the amortization of the right-of-use asset on a straight-line basis over the lease term and interest expense determined on an amortized cost basis. The lease payments are allocated between a reduction of the lease liability and interest expense.

Leasehold improvements are not unique and are retained by the lessor at the end of the lease. However, in the case of a space designed to be suitable for our specific real estate needs and if we are responsible for cost overruns, we are the accounting owner of the leasehold improvements.

We made an accounting policy election to not recognize leases with an initial term of 12 months or less within our consolidated balance sheets and to recognize those lease payments on a straight-line basis in our consolidated statements of income over the lease term.

#### **Item 7A. Quantitative and Qualitative Disclosures About Market Risk.**

We are exposed to market risk related to changes in interest rates. As of December 31, 2021, we had cash, cash equivalents and marketable securities of \$965.6 million, which consisted of cash, money market funds, commercial paper, corporate notes and a corporate equity security. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term marketable securities. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we believe an immediate 10% change in interest rates would not have a material effect on the fair market value of our investment portfolio. We have the ability to hold our investments until maturity, and therefore, we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investment portfolio.

We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we do contract with vendors that are located outside of the United States and may be subject to fluctuations in foreign currency rates. We may enter into additional contracts with vendors located outside of the United States in the future, which may increase our foreign currency exchange risk.

Inflation generally affects us by increasing our cost of labor and research, manufacturing and development costs. We believe that inflation has not had a material effect on our financial statements included elsewhere in this Annual Report on Form 10-K. However, our operations may be adversely affected by inflation in the future.

#### **Item 8. Financial Statements and Supplementary Data.**

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15, *Exhibits and Financial Statement Schedules*, of this Annual Report on Form 10-K.

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

None.

#### **Item 9A. Controls and Procedures.**

##### *Evaluation of Disclosure Controls and Procedures*

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated, as of December 31, 2021, the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. 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, or persons performing similar functions, 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 that evaluation of our disclosure controls and procedures as of December 31, 2021, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date were effective at the reasonable assurance level.



### *Management's Report on Internal Controls over Financial Reporting*

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

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

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. We continue to review our internal control over financial reporting and may from time to time make changes aimed at enhancing their effectiveness and to ensure that our systems evolve with our business.

Under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the framework in "Internal Control — Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this assessment, our senior management has concluded that the internal control over financial reporting was effective as of December 31, 2021.

Our independent registered public accounting firm, Deloitte & Touche LLP, issued an attestation report on our internal control over financial reporting. See below.

### *Changes in Internal Control over Financial Reporting*

We continuously seek to improve the efficiency and effectiveness of our internal controls. This results in refinements to processes throughout our company. There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the year ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting. During the year ended December 31, 2021, we have not experienced any material impact in our internal controls over financial reporting despite our employees working remotely due to the COVID-19 pandemic. We are continually monitoring and assessing the COVID-19 pandemic to determine any potential impacts on our internal controls over financial reporting including changes to their design and operating effectiveness.

## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Beam Therapeutics Inc.

### Opinion on Internal Control over Financial Reporting

We have audited the internal control over financial reporting of Beam Therapeutics Inc. and subsidiaries (the “Company”) as of December 31, 2021, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by COSO.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated financial statements as of and for the year ended December 31, 2021, of the Company and our report dated February 28, 2022, expressed an unqualified opinion on those financial statements.

### Basis for Opinion

The Company’s management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management’s Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company’s internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

### Definition and Limitations of Internal Control over Financial Reporting

A company’s internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company’s internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company’s assets that could have a material effect on the financial statements.

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

/s/ Deloitte & Touche LLP

Boston, Massachusetts

February 28, 2022

### Item 9B. Other Information.

None.

### Item 9C. Disclosure Regarding Foreign Jurisdictions That Prevent Inspections.

None.

## PART III

### **Item 10. Directors, Executive Officers and Corporate Governance.**

The information required by this Item 10 will be included in our definitive proxy statement to be filed with the Securities and Exchange Commission, or SEC, with respect to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference.

We have adopted a written code of business conduct and ethics, or Code, that applies to all of our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of the Code is available on the investor section of our website at [investors.beamtx.com](http://investors.beamtx.com). We intend to disclose on our website any amendments to, or waivers from, our Code that are required to be disclosed pursuant to SEC rules.

### **Item 11. Executive Compensation.**

The information required by this Item 11 will be included in the section captioned “Executive and Director Compensation” in our definitive proxy statement to be filed with the SEC with respect to our 2022 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 the sections captioned “Security Ownership of Certain Beneficial Owners and Management” and “Securities Authorized for Issuance under Equity Compensation Plans” in our definitive proxy statement to be filed with the SEC with respect to our 2022 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 the sections captioned “Certain Relationship and Related Person Transactions” and “Director Independence” in our definitive proxy statement to be filed with the SEC with respect to our 2022 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 the sections captioned “Principal Accountant Fees and Services” and “Pre-Approval by Audit Committee of Principal Accountant Services” in our definitive proxy statement to be filed with the SEC with respect to our 2022 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 F-1 of this Annual Report on Form 10-K, 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*

Exhibit Number	Description of Exhibit	Form	File Number	Date of Filing	Exhibit Number	Filed Herewith
2.1#	<a href="#">Agreement and Plan of Merger, dated February 22, 2021, among Beam Therapeutics Inc., Galileo Merger Sub I, Inc., Galileo Merger Sub II, LLC, Guide Therapeutics, Inc. (“Guide”), Shareholder Representative Services LLC, and the Guide Holders Signatory thereto</a>	10-K	001-39208	03/15/2021	2.1	
3.1	<a href="#">Fourth Amended Certificate of Incorporation of Beam Therapeutics Inc.</a>	8-K	001-39208	02/11/2020	3.1	
3.2	<a href="#">Amended and Restated By-laws of Beam Therapeutics Inc.</a>	8-K	001-39208	02/11/2020	3.2	
4.1	<a href="#">Specimen stock certificate evidencing shares of common stock</a>	S-1	333-233985	09/27/2019	4.1	
4.2	<a href="#">Amended and Restated Investors’ Rights Agreement, among Beam Therapeutics Inc. and the investors party thereto, dated November 8, 2018</a>	S-1	333-233985	09/27/2019	4.2	
4.3	<a href="#">Form of Purchase Agreement, dated as of January 16, 2021, among Beam Therapeutics Inc. and each purchaser party thereto</a>	8-K	001-39208	01/19/2021	10.1	
4.4	<a href="#">Description of Registered Securities</a>	S-3	333-254946	4/01/2021	4.11	
10.1	<a href="#">Lease, between UP 26 Landsdowne, LLC and Beam Therapeutics Inc., dated February 21, 2018</a>	S-1	333-233985	09/27/2019	10.1	
10.2	<a href="#">Indenture of Lease, between Massachusetts Institute of Technology and Beam Therapeutics Inc., dated April 24, 2019</a>	S-1	333-233985	09/27/2019	10.2	
10.3	<a href="#">Sales Agreement, dated April 1, 2021, by and between Beam Therapeutics Inc. and Jefferies LLC.</a>	8-K	001-39208	04/01/2021	1.1	
10.4#	<a href="#">License Agreement, between the President and Fellows of Harvard College and Beam Therapeutics Inc., dated June 27, 2017</a>	S-1	333-233985	09/27/2019	10.4	
10.5#	<a href="#">Amendment No. 1 to License Agreement, between the President and Fellows of Harvard College and Beam Therapeutics Inc., dated December 12, 2017</a>	10-K	001-39208	03/15/2021	10.5	
10.6#	<a href="#">Amendment No. 2 to License Agreement, between the President and Fellows of Harvard College and Beam Therapeutics Inc., dated March 27, 2020</a>	10-K	001-39208	03/15/21	10.6	
10.7#	<a href="#">License Agreement, between The Broad Institute, Inc. and Blink Therapeutics Inc., dated May 9, 2018</a>	S-1	333-233985	09/27/2019	10.5	
10.8#	<a href="#">First Amendment to License Agreement, between The Broad Institute, Inc. and Blink Therapeutics Inc., dated September 4, 2018</a>	10-K	001-39208	03/15/2021	10.8	

10.9#	<a href="#">License Agreement, between Editas Medicine, Inc. and Beam Therapeutics Inc., dated May 9, 2018</a>	S-1	333-233985	09/27/2019	10.6
10.10#	<a href="#">Letter Agreement, between Beam Therapeutics Inc., The Broad Institute, Inc., the President and Fellows of Harvard College, and Editas Medicine, Inc., dated September 26, 2018</a>	10-K	001-39208	03/15/2021	10.10
10.11	<a href="#">Letter Agreement, between the President and Fellows of Harvard College, The Broad Institute, Inc., and Beam Therapeutics Inc., dated January 7, 2021.</a>	10-K	001-39208	03/15/22021	10.11
10.12#	<a href="#">License Agreement, between Bio Palette Co., Ltd. and Beam Therapeutics Inc., dated March 27, 2019</a>	S-1	333-233985	09/27/2019	10.7
10.13+	<a href="#">Beam Therapeutics Inc. 2017 Stock Option and Grant Plan</a>	S-1/A	333-233985	01/27/2020	10.8
10.14+	<a href="#">Form of Restricted Stock Agreement under the Beam Therapeutics Inc. 2017 Stock Option and Grant Plan</a>	S-1	333-233985	09/27/2019	10.9
10.15+	<a href="#">Form of Incentive Stock Option Grant Notice under the Beam Therapeutics Inc. 2017 Stock Option and Grant Plan</a>	S-1	333-233985	09/27/2019	10.10
10.16+	<a href="#">Form of Non-Qualified Stock Option Grant Notice under the Beam Therapeutics Inc. 2017 Stock Option and Grant Plan</a>	S-1	333-233985	09/27/2019	10.11
10.17+	<a href="#">Form of Indemnification Agreement between Beam Therapeutics Inc. and its directors and officers</a>	S-1	333-233985	09/27/2019	10.12
10.18+	<a href="#">Amended and Restated Letter Agreement between Beam Therapeutics Inc. and John Evans, dated June 9, 2021</a>	10-Q	333-233985	08/10/2021	10.1
10.19+	<a href="#">Amended and Restated Employment Agreement between Beam Therapeutics Inc. and Giuseppe Ciaramella, dated January 24, 2020</a>	S-1/A	333-233985	01/27/2020	10.14
10.20+	<a href="#">Letter Agreement between Beam Therapeutics Inc. and Terry-Ann Burrell, dated January 24, 2020</a>	S-1/A	333-233985	01/27/2020	10.15
10.21+	<a href="#">Beam Therapeutics Inc. 2019 Equity Incentive Plan</a>	S-1/A	333-233985	01/27/2020	10.16
10.22+	<a href="#">Form of Incentive Stock Option Agreement under the Beam Therapeutics Inc. 2019 Equity Incentive Plan</a>	S-1/A	333-233985	01/27/2020	10.17
10.23+	<a href="#">Form of Non-Statutory Stock Option Agreement under the Beam Therapeutics Inc. 2019 Equity Incentive Plan</a>	S-1/A	333-233985	01/27/2020	10.18
10.24+	<a href="#">Form of Non-Statutory Stock Option Agreement (Non-Employee Directors) under the Beam Therapeutics Inc. 2019 Equity Incentive Plan</a>	S-1/A	333-233985	01/27/2020	10.19
10.25+	<a href="#">Form of Restricted Stock Unit Award Agreement under the Beam Therapeutics Inc. 2019 Equity Incentive Plan</a>	10-K	001-39208	3/15/2021	10.25
10.26+	<a href="#">Form of Restricted Stock Award Agreement under the Beam Therapeutics Inc. 2019 Equity Incentive Plan</a>	10-K	001-39208	03/15/2021	10.26
10.27+	<a href="#">Amended and Restated Beam Therapeutics Inc. 2019 Employee Stock Purchase Plan</a>				X
10.28+	<a href="#">Beam Therapeutics Inc. 2019 Cash Incentive Plan</a>	S-1/A	333-233985	01/27/2020	10.21
10.29+	<a href="#">Amended and Restated Beam Therapeutics Inc. Non-Employee Director Compensation Policy, dated June 10, 2021</a>	10-Q	001-39208	08/10/2021	10.2
10.30	<a href="#">Lease Agreement between Beam Therapeutics Inc. and ARE-NC Region No. 14, LLC</a>	10-Q	001-39208	08/12/2020	10.1

10.31	<a href="#">Amendment No. 1 to Indenture of Lease, between Massachusetts Institute of Technology and Beam Therapeutics Inc., dated April 14, 2020</a>					X
10.32	<a href="#">Amendment No. 2 to Indenture of Lease, between Massachusetts Institute of Technology and Beam Therapeutics Inc., dated November 17, 2020</a>					X
10.33	<a href="#">Amendment No. 3 to Indenture of Lease, between Massachusetts Institute of Technology and Beam Therapeutics Inc., dated August 24, 2021</a>					X
10.34	<a href="#">Amendment No. 1 to Sales Agreement, dated July 7, 2021, by and between Beam Therapeutics Inc. and Jefferies LLC</a>	8-K	001-39208	07/07/2021	1.1	
21.1	<a href="#">List of Subsidiaries of Beam Therapeutics Inc.</a>					X
23.1	<a href="#">Consent of Deloitte &amp; Touche LLP</a>					X
31.1	<a href="#">Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.</a>					X
31.2	<a href="#">Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.</a>					X
32.1*	<a href="#">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.</a>					X
32.2*	<a href="#">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.</a>					X
101.INS	Inline XBRL Instance Document - the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)					X

# Portions of this exhibit have been omitted because the Registrant has determined they are not material and are they type that the Registrant treats as private or confidential.

+ Indicates management contract or compensatory plan.

\* This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

**Item 16. Form 10-K Summary**

None.





## INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

<a href="#">Report of independent registered public accounting firm (PCAOB ID No. 34)</a>	F-2
<a href="#">Consolidated balance sheets</a>	F-4
<a href="#">Consolidated statements of operations and other comprehensive loss</a>	F-5
<a href="#">Consolidated statements of redeemable convertible preferred stock and stockholders' equity (deficit)</a>	F-6
<a href="#">Consolidated statements of cash flows</a>	F-7
<a href="#">Notes to consolidated financial statements</a>	F-9

## REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Beam Therapeutics Inc.

### Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Beam Therapeutics Inc. and subsidiaries (the "Company") as of December 31, 2021 and 2020, the related consolidated statements of operations and other comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit), and cash flows, for each of the three years in the period ended December 31, 2021, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with accounting principles generally accepted in the United States of America.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control — Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 28, 2022, expressed an unqualified opinion on the Company's internal control over financial reporting.

### 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 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. 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.

### Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current-period audit of the financial statements that was communicated or required to be communicated to the audit committee and that (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

#### ***Guide Asset Acquisition – Contingent Consideration Liabilities— Refer to Notes 2, 4, and 8 to the financial statements***

##### *Critical Audit Matter Description*

In February 2021, the Company completed the acquisition of Guide Therapeutics, Inc. ("Guide") and the transaction was accounted for as an asset acquisition. The Company may be required to make milestone payments to the former stockholders and optionholders of Guide in the form of the Company's common stock based on the achievement of certain product and technology milestones. As of December 31, 2021 the Company has recorded a liability for the acquisition-related contingent consideration, which is recorded at fair value using unobservable inputs by applying a probability-based valuation model.

The key assumptions management used in the valuation model are the probability and timing of achievement of the product and technology milestones, which are not observable in the market, thus representing Level 3 measurements within the fair value hierarchy.

Given that the valuation of the Guide contingent consideration liability is based on unobservable inputs and is sensitive to changes in the probability and timing of achievement of the milestones, auditing these key assumptions required a high degree of auditor judgment and an increased extent of effort, including the need to involve our fair value specialists.

##### *How the Critical Audit Matter Was Addressed in the Audit*

Our audit procedures related to the Guide contingent consideration liability included the following, among others:

- We tested the effectiveness of controls over management's review of the inputs and assumptions used in the valuation of the Guide contingent consideration liability, including the probability and timing of achievement of the product and technology milestones.

- We inquired of management and the Company's scientific personnel to understand each milestone and the underlying assumptions, including current progress of development and underlying data associated with development efforts and timing of the related milestones.
- We read the Guide acquisition agreements to understand the terms of the contingent consideration obligation and compared the contract terms to the valuation model to evaluate consistency.
- With the assistance of our fair value specialists, we evaluated the reasonableness of the valuation methodology.
- We also evaluated the reasonableness of management's assumptions of the probability and timing of achievement of the product and technology milestones by reviewing (1) internal communications to management and the board of directors, (2) external communications made by management to analysts and investors, and (3) other external sources.
- We evaluated whether management's assumptions used for the technology and product milestones were consistent with evidence obtained in other areas of the audit.

/s/ Deloitte & Touche LLP

Boston, Massachusetts

February 28, 2022

We have served as the Company's auditor since 2017.

**Beam Therapeutics Inc.**  
**Consolidated Balance Sheets**  
(in thousands, except share and per share amounts)

	December 31,	
	2021	2020
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 559,994	\$ 162,171
Marketable securities	405,653	137,500
Collaboration receivable	300,000	—
Prepaid expenses and other current assets	7,360	8,650
Total current assets	1,273,007	308,321
Property and equipment, net	84,258	38,513
Restricted cash	12,746	14,840
Operating lease right-of-use assets	102,718	86,859
Other assets	1,724	3,144
Total assets	\$ 1,474,453	\$ 451,677
<b>Liabilities and stockholders' equity</b>		
Current liabilities:		
Accounts payable	\$ 7,474	\$ 6,314
Accrued expenses and other current liabilities	28,921	18,463
Accrued sub-license fees	38,743	—
Derivative liabilities	42,200	71,200
Current portion of deferred revenue	86,270	24
Current portion of lease liability	7,540	4,218
Current portion of equipment financing liability	2,287	2,118
Total current liabilities	213,435	102,337
Long-term lease liability	134,810	96,014
Long-term equipment financing liability	3,007	5,294
Contingent consideration liabilities	31,367	—
Long-term portion of deferred revenue	262,303	394
Other liabilities	2,793	2,077
Total liabilities	647,715	206,116
Commitments and contingencies (See Note 7, <i>Leases</i> , Note 9, <i>License agreements</i> and Note 10, <i>Collaboration and license agreements</i> )		
Stockholders' equity:		
Preferred stock, \$0.01 par value; 25,000,000 shares authorized, and no shares issued or outstanding at December 31, 2021 and 2020, respectively	—	—
Common stock, \$0.01 par value; 250,000,000 shares authorized, 68,581,251 and 58,446,016 issued, and 68,389,425 and 57,254,178 outstanding at December 31, 2021 and 2020, respectively	684	573
Additional paid-in capital	1,594,378	642,633
Accumulated other comprehensive (loss) income	(50)	(9)
Accumulated deficit	(768,274)	(397,636)
Total stockholders' equity	826,738	245,561
Total liabilities, redeemable convertible preferred stock, and stockholders' equity	\$ 1,474,453	\$ 451,677

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

**Beam Therapeutics Inc.**  
**Consolidated Statements of Operations and Other Comprehensive Loss**  
(in thousands, except share and per share amounts)

	Years Ended December 31,		
	2021	2020	2019
License and collaboration revenue	\$ 51,844	\$ 24	\$ 18
Operating expenses:			
Research and development	387,087	103,179	54,619
General and administrative	57,222	29,605	20,553
Total operating expenses	<u>444,309</u>	<u>132,784</u>	<u>75,172</u>
Loss from operations	(392,465)	(132,760)	(75,154)
Other income (expense):			
Change in fair value of derivative liabilities	(1,000)	(63,400)	(5,400)
Change in fair value of non-controlling equity investments	17,690	517	—
Change in fair value of contingent consideration liabilities	5,146	—	—
Interest and other income (expense), net	(9)	1,051	2,228
Total other income (expense)	<u>21,827</u>	<u>(61,832)</u>	<u>(3,172)</u>
Net loss	<u>\$ (370,638)</u>	<u>\$ (194,592)</u>	<u>\$ (78,326)</u>
Unrealized (loss) gain on marketable securities	(41)	(25)	16
Comprehensive loss	<u>\$ (370,679)</u>	<u>\$ (194,617)</u>	<u>\$ (78,310)</u>
Reconciliation of net loss to net loss attributable to common stockholders:			
Net loss	(370,638)	(194,592)	(78,326)
Accretion of redeemable convertible preferred stock to redemption value, including dividends on preferred stock	—	(1,277)	(12,714)
Net loss attributable to common stockholders	<u>\$ (370,638)</u>	<u>\$ (195,869)</u>	<u>\$ (91,040)</u>
Net loss per common share attributable to common stockholders, basic and diluted	<u>\$ (5.77)</u>	<u>\$ (4.19)</u>	<u>\$ (14.05)</u>
Weighted-average common shares used in net loss per share attributable to common stockholders, basic and diluted	<u>64,227,676</u>	<u>46,733,221</u>	<u>6,479,591</u>

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

**Beam Therapeutics Inc.**  
**Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)**  
(in thousands, except share amounts)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balance at December 31, 2018	119,308,387	\$ 251,434	5,565,368	\$ 56	\$ 7,256	\$ —	\$ (124,718)	\$ (117,406)
Issuance of Series B redeemable convertible preferred stock, net of issuance costs of \$95	11,308,397	37,901	—	—	—	—	—	—
Accretion of redeemable convertible preferred stock to redemption value	—	12,714	—	—	(12,714)	—	—	(12,714)
Vesting of restricted common stock	—	—	1,559,126	15	(15)	—	—	—
Exercise of common stock options	—	—	184,966	2	183	—	—	185
Issuance of common stock related to license agreement	—	—	16,725	—	113	—	—	113
Stock-based compensation	—	—	—	—	7,028	—	—	7,028
Other comprehensive income (loss)	—	—	—	—	—	16	—	16
Net loss	—	—	—	—	—	—	(78,326)	(78,326)
Balance at December 31, 2019	130,616,784	\$ 302,049	7,326,185	\$ 73	\$ 1,851	\$ 16	\$ (203,044)	\$ (201,104)
Accretion of redeemable convertible preferred stock to redemption value	—	1,277	—	—	(1,277)	—	—	(1,277)
Conversion of redeemable convertible preferred stock to common stock upon closing of initial public offering	(130,616,784)	(303,326)	29,127,523	291	303,035	—	—	303,326
Issuance of common stock from initial public offering, net of issuance costs of \$18.7 million	—	—	12,176,471	122	188,201	—	—	188,323
Issuance of common stock from October 2020 public offering, net of issuance costs of \$8.5 million	—	—	5,750,000	58	126,566	—	—	126,624
Issuance of common stock related to license agreements	—	—	375,307	4	5,747	—	—	5,751
Vesting of restricted common stock	—	—	1,638,968	16	(16)	—	—	—
Stock-based compensation	—	—	—	—	15,380	—	—	15,380
Exercise of common stock options	—	—	859,724	9	3,146	—	—	3,155
Other comprehensive income (loss)	—	—	—	—	—	(25)	—	(25)
Net loss	—	—	—	—	—	—	(194,592)	(194,592)
Balance at December 31, 2020	—	\$ —	57,254,178	\$ 573	\$ 642,633	\$ (9)	\$ (397,636)	\$ 245,561
Issuance of common stock from private placement, net of issuance costs of \$8.0 million	—	—	2,795,700	28	251,977	—	—	252,005
Issuance of common stock from At-the-Market offering, net of issuance costs of \$14.6 million	—	—	4,907,195	49	496,574	—	—	496,623
Issuance of common stock for success payment liability	—	—	349,650	4	29,996	—	—	30,000
Issuance of common stock to acquire Guide	—	—	1,087,153	10	120,022	—	—	120,032
Vesting of restricted common stock	—	—	1,020,887	10	(10)	—	—	—
Stock-based compensation	—	—	—	—	43,570	—	—	43,570
Exercise of common stock options	—	—	974,662	10	9,616	—	—	9,626
Other comprehensive income (loss)	—	—	—	—	—	(41)	—	(41)
Net loss	—	—	—	—	—	—	(370,638)	(370,638)
Balance at December 31, 2021	—	\$ —	68,389,425	\$ 684	\$ 1,594,378	\$ (50)	\$ (768,274)	\$ 826,738

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

**Beam Therapeutics Inc.**  
**Consolidated Statements of Cash Flows**  
(in thousands)

	Years Ended December 31,		
	2021	2020	2019
<b>Operating activities</b>			
Net loss	\$ (370,638)	\$ (194,592)	\$ (78,326)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	7,451	4,735	3,503
Amortization of investment discount (premium)	(75)	118	(920)
In-process research and development charge	154,953	—	—
Stock-based compensation expense	43,570	15,380	7,028
Change in operating lease right-of-use assets	8,990	4,737	1,904
Non-cash research and development license expense, net	—	5,651	113
Change in fair value of derivative liabilities	1,000	63,400	5,400
Change in fair value of contingent consideration liabilities	(5,146)	—	—
Change in fair value of non-controlling equity investments	(17,690)	(517)	—
Other, net	63	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	746	(5,726)	(1,258)
Other long-term assets	(197)	(154)	(634)
Accounts payable	818	60	4,092
Accrued expenses and other liabilities	43,914	7,035	3,571
Operating lease liabilities	16,028	3,151	(2,535)
Collaboration receivable	(300,000)	—	—
Deferred revenue	348,156	—	—
Financing milestone liabilities	—	—	(13,750)
Other long-term liabilities	1,789	981	(191)
Net cash used in operating activities	(66,268)	(95,741)	(72,003)
<b>Investing activities</b>			
Purchases of property and equipment	(46,811)	(16,357)	(12,518)
Purchases of marketable securities	(777,223)	(281,612)	(129,760)
Maturities of marketable securities	529,270	198,596	76,069
Net cash acquired from Guide	620	—	—
Purchase of non-controlling equity investment	—	(750)	(450)
Net cash used in investing activities	(294,144)	(100,123)	(66,659)
<b>Financing activities</b>			
Proceeds from issuance of Series B Preferred Stock, net	—	—	37,901
Proceeds from initial public offering, net of underwriting discount	—	192,510	—
Proceeds from October 2020 public offering, net of underwriting discount	—	127,018	—
Proceeds from issuance of common shares, net of commissions	757,449	—	—
Payment of initial and follow-on equity offering costs	(8,816)	(2,059)	(2,521)
Proceeds from equipment financings	—	3,267	6,178
Repayment of equipment financings	(2,118)	(1,569)	(464)
Proceeds from exercise of stock options	9,626	3,155	185
Net cash provided by financing activities	756,141	322,322	41,279
Net increase (decrease) in cash, cash equivalents and restricted cash	395,729	126,458	(97,383)
Cash, cash equivalents and restricted cash—beginning of period	177,011	50,553	147,936
Cash, cash equivalents and restricted cash—end of period	<u>\$ 572,740</u>	<u>\$ 177,011</u>	<u>\$ 50,553</u>

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

**Beam Therapeutics Inc.**  
**Consolidated statements of cash flows (continued)**  
(in thousands)

	Years Ended December 31,		
	2021	2020	2019
<b>Supplemental disclosure of cash flow information:</b>			
Cash paid for interest	\$ 567	\$ 561	\$ 187
<b>Supplemental disclosure of non-cash investing and financing activities:</b>			
Conversion of redeemable convertible preferred stock to common stock upon closing of the initial public offering	\$ —	\$ 303,326	\$ —
Property and equipment additions in accounts payable and accrued expenses	\$ 9,264	\$ 5,067	\$ 2,465
Receipt of common stock in exchange for technology license	\$ —	\$ 100	\$ 460
Operating lease liabilities arising from obtaining right-of-use assets	\$ 25,925	\$ 74,723	\$ 6,221
Issuance of common stock for research and development licenses	\$ —	\$ 5,751	\$ 113
Equity issuance costs in accounts payable and accrued expenses	\$ 5	\$ —	\$ 593
Fair value of common stock issued to settle success payment liability	\$ 30,000	\$ —	\$ —
Contingent consideration liabilities assumed in asset acquisition	\$ 36,513	\$ —	\$ —
Fair value of equity instruments issued in connection with asset acquisition	\$ 120,032	\$ —	\$ —
Accretion of redeemable convertible preferred stock to redemption value, including dividends on preferred stock	\$ —	\$ 1,277	\$ 12,714

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



## **1. Nature of the business and basis of presentation**

### ***Organization***

Beam Therapeutics Inc., which we refer to herein as the “Company” or “Beam,” is a biotechnology company committed to establishing the leading, fully integrated platform for precision genetic medicines. Beam’s vision is to provide life-long cures to patients suffering from genetic diseases. The Company was incorporated on January 25, 2017 as a Delaware corporation and began operations in July 2017. Its principal offices are in Cambridge, Massachusetts.

In February 2021, the Company entered into an Agreement and Plan of Merger, or the Guide Merger Agreement, to acquire Guide Therapeutics, Inc., or Guide. Pursuant to the Guide Merger Agreement, the Company paid Guide’s former stockholders and optionholders upfront consideration in an aggregate amount of \$120.0 million, excluding customary purchase price adjustments, in shares of its common stock, based upon the volume-weighted average price of the Company’s common stock over the ten trading-day period ending on February 19, 2021. In addition, Guide’s former stockholders and optionholders are eligible to receive up to an additional \$100.0 million in technology milestone payments and \$220.0 million in product milestone payments, payable in the Company’s common stock.

### ***Liquidity and capital resources***

Since its inception, the Company has devoted substantially all of its resources to building its base editing platform and advancing development of its portfolio of programs, establishing and protecting its intellectual property, conducting research and development activities, making arrangements to conduct manufacturing activities with contract manufacturing organizations, research and development costs including preclinical studies and IND-enabling studies, organizing and staffing the Company, maintaining its facilities and new facility build-outs, business planning, raising capital and providing general and administrative support for these operations. The Company is also in the process of developing internal manufacturing capabilities. The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry including, but not limited to, technical risks associated with the successful research, development and manufacturing of product candidates, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Current and future programs will require significant research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure. Even if the Company’s product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

In February 2020, the Company completed its initial public offering, or IPO, in which the Company issued and sold 12,176,471 shares of its common stock, including 1,588,235 shares pursuant to the full exercise of the underwriters’ option to purchase additional shares, at a public offering price of \$17.00 per share, for aggregate gross proceeds of \$207.0 million. The Company received approximately \$188.3 million in net proceeds after deducting underwriting discounts and offering expenses payable by the Company. In connection with the IPO, all outstanding shares of the Company’s redeemable convertible preferred stock converted into 29,127,523 shares of its common stock.

In October 2020, the Company issued and sold 5,750,000 shares of its common stock, including 750,000 shares pursuant to the full exercise of the underwriters’ option to purchase additional shares, at a public offering price of \$23.50 per share, for aggregate gross proceeds of \$135.1 million. The Company received approximately \$126.6 million in net proceeds after deducting underwriting discounts and offering expenses payable by the Company.

On January 16, 2021, the Company entered into a Securities Purchase Agreement with certain purchasers, pursuant to which the Company agreed to sell and issue to the purchasers, in a private placement, shares of common stock of the Company. The closing of the private placement occurred on January 21, 2021. The Company issued and sold 2,795,700 shares of its common stock at a purchase price of \$93.00 per share for aggregate gross proceeds of \$260.0 million, before deducting fees to the placement agents and other offering expenses payable by the Company (See Note 11, *Preferred and common stock*). The Company received approximately \$252.0 million in net proceeds after deducting fees to the placement agents and offering expenses payable by the Company.

In April 2021, the Company entered into an at the market, or ATM, sales agreement, or the Sales Agreement, with Jefferies LLC, or Jefferies, pursuant to which the Company was entitled to offer and sell, from time to time at prevailing market prices, shares of the Company’s common stock having aggregate gross proceeds of up to \$300.0 million. The Company agreed to pay Jefferies a commission of up to 3.0% of the aggregate gross sale proceeds of any shares sold by Jefferies under the Sales Agreement. Between April and July 2021, the Company has sold 2,908,009 shares of its common stock under the Sales Agreement at an average price of \$103.16 per share for aggregate gross proceeds of \$300.0 million, before deducting commissions and offering expenses payable by the Company.

In July 2021, the Company and Jefferies entered into an amendment to the Sales Agreement to provide for an increase in the aggregate offering amount under the Sales Agreement, such that as of July 7, 2021, the Company may offer and sell shares of common stock having an aggregate offering price of an additional \$500.0 million. As of December 31, 2021, the Company has sold 1,999,186 additional shares of its common stock under the amended Sales Agreement at an average price of \$105.65 per share for aggregate gross proceeds of \$211.2 million, before deducting commissions and offering expenses payable by the Company, resulting in an aggregate of \$511.2 million in gross proceeds received under the Sales Agreement as of December 31, 2021.

In June 2021, the Company entered into a research collaboration agreement, or the Apellis Agreement, with Apellis Pharmaceuticals, Inc., or Apellis, focused on the use of certain of its base editing technology to discover new treatments for complement system-driven diseases. Pursuant to the Apellis Agreement, the Company received an upfront payment of \$50.0 million in July 2021. The Company is also eligible to receive an additional payment of \$25.0 million on June 30, 2022, the one-year anniversary of the effective date of the Apellis Agreement.

In October 2021, the Company entered into an option and license agreement, or the Sana Agreement, with Sana Biotechnology, Inc., or Sana, pursuant to which the Company granted Sana non-exclusive commercial rights to its CRISPR Cas12b nuclease system for certain *ex vivo* engineered cell therapy programs. Pursuant to this agreement, the Company received an upfront payment of \$50.0 million in October 2021.

In December 2021, the Company entered into a research collaboration agreement, or the Pfizer Agreement, with Pfizer Inc., or Pfizer, focused on *in vivo* base editing programs for three targets for rare genetic diseases of the liver, muscle and central nervous system. Under the terms of the Pfizer Agreement, the Company will conduct all research activities through development candidate selection for three undisclosed targets, which are not included in the Company's existing programs. Pursuant to this agreement, the Company received an upfront payment of \$300.0 million in January 2022.

Since its inception, the Company has incurred substantial losses and had an accumulated deficit of \$768.3 million as of December 31, 2021. The Company expects to generate operating losses and negative operating cash flows for the foreseeable future.

The Company expects that its cash, cash equivalents, and marketable securities as of December 31, 2021 of \$965.6 million will be sufficient to fund its operations for at least the next 12 months from the date of issuance of these financial statements. The Company will need additional financing to support its continuing operations and pursue its growth strategy. Until such time as the Company can generate significant revenue from product sales, if ever, it expects to finance its operations through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. The Company may be unable to raise additional funds or enter into such other agreements when needed on favorable terms or at all. The inability to raise capital as and when needed would have a negative impact on the Company's financial condition and its ability to pursue its business strategy. The Company will need to generate significant revenue to achieve profitability, and it may never do so.

#### **COVID-19-related significant risks and uncertainties**

With the ongoing concerns related to the COVID-19 pandemic during 2021, the Company has maintained and expanded its business continuity plans to address and mitigate the impact of the COVID-19 pandemic on its business. In March 2020, to protect the health of its employees, and their families and communities, the Company restricted access to its offices to personnel who performed critical activities that must be completed on-site, limited the number of such personnel that could be present at its facilities at any one time, and requested that most of its employees work remotely. In May 2021, as certain states eased restrictions, the Company established new protocols to better allow its full laboratory staff access to the Company's facilities. These protocols included several shifts working over a seven-day-week protocol. In June 2021, as certain states continued to ease restrictions, the Company started to allow its entire workforce the ability to work on-site at the Company's facilities, with fewer restrictions, particularly for vaccinated employees. The Company expects to continue incurring additional costs to ensure it adheres to the guidelines instituted by the Centers for Disease Control and Prevention, or CDC, and to provide a safe working environment to its onsite employees.

The extent to which the COVID-19 pandemic impacts the Company's business, its corporate development objectives, results of operations and financial condition, and the value of and market for its common stock, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements, and the effectiveness of actions taken globally to contain and treat the disease. Disruptions to the global economy and supply chain, disruption of global healthcare systems, and other significant impacts of the COVID-19 pandemic could have a material adverse effect on the Company's business, financial condition, results of operations and growth prospects.

While the COVID-19 pandemic did not significantly impact the Company's business or results of operations during the twelve months ended December 31, 2021, the length and extent of the pandemic, its consequences, and containment efforts will determine the future impact on the Company's operations and financial condition.

## 2. Summary of significant accounting policies

### *Basis of presentation*

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

### *Principles of consolidation*

The accompanying consolidated financial statements include the results of operations of the Company and its wholly-owned subsidiaries. All intercompany transactions and balances have been eliminated in consolidation.

In September 2021, the Company's wholly-owned subsidiary Blink Therapeutics Inc., or Blink, merged with and into Beam, such that Blink's separate corporate existence ceased and Beam Therapeutics Inc. continued as the surviving corporation.

### *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, liabilities, revenues and expenses, and the disclosure of contingent assets and liabilities as of and during the reporting period. The Company bases its estimates and assumptions on historical experience when available and on various factors that it believes to be reasonable under the circumstances. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, incremental borrowing rate used in the calculation of lease liabilities, research and development expenses, the fair values of common stock, stock-based compensation, contingent consideration liabilities, success payments and certain judgements regarding revenue recognition. Actual results could differ from these estimates.

### *Cash, cash equivalents, and restricted cash*

Cash and cash equivalents consist of standard checking accounts, money market accounts, and all highly liquid investments with a remaining maturity of three months or less at the date of purchase. Restricted cash represents collateral provided for letters of credit issued as security deposits in connection with the Company's leases of its corporate and manufacturing facilities.

The following table reconciles cash, cash equivalents, and restricted cash reported within the Company's consolidated balance sheets to the total of the amounts shown in the consolidated statements of cash flows (in thousands):

	December 31,		
	2021	2020	2019
Cash and cash equivalents	\$ 559,994	\$ 162,171	\$ 37,221
Restricted cash	12,746	14,840	13,332
Total cash, cash equivalents, and restricted cash	<u>\$ 572,740</u>	<u>\$ 177,011</u>	<u>\$ 50,553</u>

### *Marketable securities*

The Company classifies marketable securities with a remaining maturity when purchased of greater than three months as available-for-sale. Available-for-sale securities are maintained by the Company's investment managers and consist of commercial paper, high-grade corporate notes, U.S. Treasury securities and government securities. Available-for-sale securities are carried at fair value with the unrealized gains and losses included in accumulated other comprehensive (loss) income as a component of stockholders' equity until realized. Any premium or discount arising at purchase is amortized and/or accreted to interest income and/or expense over the life of the instrument. Realized gains and losses are determined using the specific identification method and are included in interest and other income (expense), net.

### *Corporate equity securities*

The Company classifies investments in equity securities that have a readily determinable fair value as marketable securities in the Company's consolidated balance sheets. The Company's marketable securities are stated at fair value. Typically, the fair value of these securities is based on a quoted price for an identical equity security. The Company also holds an investment in privately issued corporate equity securities, which are accounted for as investments in equity securities. This investment does not have a readily determinable fair value and the Company values the investment based on the cost of the equity securities adjusted for observable market transactions or impairments, if any, and records any changes in value through earnings. The Company records changes in the fair value of its equity securities in other income (expense), net in its consolidated statements of operations and other comprehensive loss.

### **Concentrations of credit risk**

Financial instruments that are potentially subject to significant concentration of credit risk consist primarily of cash, cash equivalents, marketable securities, and restricted cash. The Company attempts to minimize the risk related to marketable securities by working with highly rated financial institutions that invest in a broad and diverse range of financial instruments as defined the Company. The Company has established guidelines relative to credit ratings and maturities intended to safeguard principal balances and maintain liquidity. The Company maintains its funds in accordance with its investment policy, which defines allowable investments, specifies credit quality standards and is designed to limit credit exposure to any single issuer.

### **Guarantees and indemnifications**

As permitted under Delaware law, the Company indemnifies its officers, directors, consultants, and employees for certain events or occurrences that happen by reason of the relationship with, or position held at, the Company. For the twelve months ended December 31, 2021, 2020 and 2019, the Company had not experienced any losses related to these indemnification obligations, and no claims were outstanding. The Company does not expect significant claims related to these indemnification obligations and, consequently, concluded that the fair value of these obligations is negligible, and no related reserves were established.

### **Equity issuance costs**

The Company capitalizes incremental legal, professional, accounting and other third-party fees that were directly associated with its stock offerings as other non-current assets until the offerings are consummated. Upon consummation, these costs are recorded in stockholders' equity as a reduction of additional paid-in-capital generated as a result of the offerings. As of December 31, 2021 and 2020, there were no deferred offering costs.

### **Fair value of financial instruments**

ASC Topic 820, *Fair Value Measurement*, or ASC 820, establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from independent sources. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the assets or liability and are developed based on the best information available in the circumstances. ASC 820 identifies fair value as the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. As a basis for considering market participant assumptions in fair value measurements, ASC 820 establishes a three-tiered value hierarchy that distinguishes between the following:

Level 1—Quoted market prices in active markets for identical assets or liabilities.

Level 2—Inputs other than Level 1 inputs that are either directly or indirectly observable, such as quoted market prices, interest rates and yield curves.

Level 3—Unobservable inputs for the asset or liability (i.e. supported by little or no market activity). Level 3 inputs include management's own assumptions about the assumptions that market participants would use in pricing the asset or liability (including assumptions about risk).

To the extent the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair values requires more judgement. Accordingly, the degree of judgement exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

There have been no changes to the valuation methods utilized during the years ended December 31, 2021 and 2020. The Company evaluates transfers between levels at the end of each reporting period.

### **Property and equipment**

Property and equipment are stated at cost less accumulated depreciation. Depreciation expense is recognized using the straight-line method over the estimated useful life of each asset as follows:

<u>Asset category</u>	<u>Estimated useful life</u>
Computer equipment and software	3 years
Laboratory equipment and office furniture	5 years
Leasehold improvements	Shorter of useful life or remaining term

Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in interest and other income (expense). Expenditures for repairs and maintenance are charged to expense as incurred.

### ***Impairment of long-lived assets***

The Company evaluates its long-lived assets, which consist primarily of property and equipment and operating lease right-of-use assets, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the asset. There were no impairment losses recognized during the years ended December 31, 2021, 2020 and 2019.

### ***Freestanding financial instruments and derivatives***

Pursuant to a license agreement between the President and Fellows of Harvard College, or Harvard, and the Company, or the Harvard License Agreement, and a license agreement with The Broad Institute, Inc., or Broad Institute, and the Company, or the Broad License Agreement, (see Note 9, *License Agreements*), the Company is required to make success payments to Harvard and Broad Institute based on the achievement of specified multiples of the initial weighted average value of the Company's redeemable convertible Series A-1 Preferred Stock and the Company's redeemable convertible Series A-2 Preferred Stock, or together the Series A Preferred, at specified valuation dates, payable in cash or Company common stock. Subsequent to the IPO, the amount of the success payments is based on the market value of Beam's common stock. The success payments are accounted for under ASC 815, *Derivatives and Hedging* and were initially recorded at fair value with a corresponding charge to research and development expense. The liabilities are marked to market at each balance sheet date with all changes in value recognized in other income (expense), in the consolidated statement of operations and other comprehensive loss. The Company will continue to adjust the liability for changes in fair value until the earlier of the achievement or expiration of the success payment obligation. To determine the estimated fair value of the success payments, the Company used a Monte Carlo simulation model, which models the value of the liability based on several key variables, including probability of event occurrence, timing of event occurrence, as well as the value of the Series A Preferred, prior to the IPO, and the value of the Company's common stock, subsequent to the IPO.

### ***Leases and rent expense***

On January 1, 2019, the Company adopted ASU No. 2016-02, *Leases (Topic 842)*, or ASC 842. Under the standard the Company accounts for leases using a right-of-use, or ROU, model, which recognizes that, at the date of commencement, a lessee has a financial obligation to make lease payments to the lessor for the right to use the underlying asset during the lease term.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as ROU assets and short-term and long-term lease liabilities, as applicable. ROU assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent its obligation to make lease payments arising from the lease. The Company typically only includes an initial lease term in its assessment of a lease arrangement. It also considers termination options and factors those into the determination of lease payments. Options to renew a lease are not included in the assessment unless there is reasonable certainty that the Company will renew.

Operating lease liabilities and their corresponding ROU assets are recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the ROU asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate, which reflects the fixed rate at which it could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. Lease expense for lease payments is recognized on a straight-line basis over the lease term.

The Company is required to pay fees for operating expenses in addition to monthly base rent for certain operating leases (non-lease components). The Company has elected the practical expedient which allows non-lease components to be combined with lease components for all asset classes. Variable non-lease components are not included within the lease right-of-use asset and lease liability on the consolidated balance sheet, and instead are reflected as expense in the period they are paid.

Leasehold improvements are not unique and are retained by the lessor at the end of the lease. However, in the case of a space designed to be suitable for the Company's specific real estate needs and if the Company is responsible for cost overruns, the Company is the accounting owner of the leasehold improvements and costs associated are capitalized.

The Company's real estate operating leases provide for scheduled annual rent increases throughout the lease terms. The Company recognizes the effects of the scheduled rent increases on a straight-line basis over the full terms of the lease. Tenant improvement allowances, if any, provided by a landlord are recorded as a reduction of the ROU asset related to that lease.

### ***Asset acquisitions***

In 2018, the Company adopted ASU 2017-01, *Business Combinations*, or ASU 2017-01, which clarified the definition of a business. The Company measures and recognizes asset acquisitions that are not deemed to be business combinations based on the cost to acquire the assets, which includes transaction costs, and the consideration is allocated to the items acquired based on a relative fair value methodology. Goodwill is not recognized in asset acquisitions. In an asset acquisition, the cost allocated to acquire in-process research and development with no alternative future use is charged to research and development expense at the acquisition date.

At the time of acquisition, the Company determines if a transaction should be accounted for as a business combination or acquisition of assets.

#### **Contingent consideration liabilities**

The Company may be required to make milestone payments to the former stockholders and optionholders of Guide in the form of its common stock based on the achievement of certain product and technology milestones. The payments are accounted for under ASC 480, *Distinguishing Liabilities from Equity*. These contingent consideration liabilities are carried at fair value which was estimated by applying a probability-based model, which utilized inputs primarily based upon the achievement and related timing of certain product and technology milestones that were unobservable in the market. The estimated fair value of contingent consideration liabilities, initially measured and recorded on the acquisition date, are considered to be a Level 3 measurement and are reviewed quarterly, or whenever events or circumstances occur that indicate a change in fair value. The contingent consideration liabilities are recorded at fair value at the end of each reporting period with changes in estimated fair values recorded in other income (expense) in the consolidated statements of operations and other comprehensive loss.

The estimated fair value is determined based on probability adjusted discounted cash flow model that include significant estimates and assumptions pertaining to technology and product development. Significant changes in any of the probabilities of success or in the probabilities as to the periods in which milestones would be achieved would result in a significantly higher or lower fair value measurement. The Company will continue to adjust the liabilities for changes in fair value until the earlier of the achievement or expiration of the obligations.

#### **Revenue recognition**

The Company recognizes revenue in accordance with ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* and its related amendments, or, collectively, ASC 606.

At inception, the Company determines whether contracts are within the scope of ASC 606 or other topics. For contracts that are determined to be within the scope of ASC 606, revenue is recognized when a customer obtains control of promised goods or services. The amount of revenue recognized reflects the consideration to which the Company expects to be entitled to receive in exchange for these goods and services. To achieve this core principle, the Company applies the following five steps: (i) identify the contract with the customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when the performance obligation is satisfied. The Company only applies the five-step model to contracts when it determines that collection of substantially all consideration for goods and services that are transferred is probable based on the customer's intent and ability to pay the promised consideration.

Performance obligations promised in a contract are identified based on the goods and services that will be transferred to the customer that are both capable of being distinct and are distinct in the context of the contract. To the extent a contract includes multiple promised goods and services, the Company applies judgment to determine whether promised goods and services are both capable of being distinct and are distinct in the context of the contract. If these criteria are not met, the promised goods and services are accounted for as a combined performance obligation.

The transaction price is determined based on the consideration to which the Company will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration, the Company estimates the amount of variable consideration that should be included in the transaction price utilizing either the expected value method or the most likely amount method, depending on the nature of the variable consideration. Variable consideration is included in the transaction price if, in management's judgment, it is probable that a significant future reversal of cumulative revenue under the contract will not occur. Any estimates, including the effect of the constraint on variable consideration, are evaluated at each reporting period for any changes. Determining the transaction price requires significant judgment and is discussed in further detail for each of the Company's license and collaboration agreements in Note 10, *Collaboration and license agreements*.

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price to each performance obligation on a relative standalone selling price basis unless the transaction price is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct service that forms part of a single performance obligation. The consideration to be received is allocated among the separate performance obligations based on relative standalone selling prices. Determining the standalone selling price requires significant judgment and is discussed in further detail for each of the Company's license and collaboration agreements in Note 10, *Collaboration and license agreements*.

The Company satisfies performance obligations either over time or at a point in time. Revenue is recognized over time if either (i) the customer simultaneously receives and consumes the benefits provided by the entity's performance, (ii) the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or (iii) the entity's performance does not create an asset with an alternative use to the entity and the entity has an enforceable right to payment for performance completed to date. If the entity does not satisfy a performance obligation over time, the related performance obligation is satisfied at a point in time by transferring the control of a promised good or service to a customer.

Licenses of intellectual property, or IP: If the license to the Company's IP is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from consideration allocated to the license when the license is transferred to the customer and the customer can use and benefit from the licenses. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. Determining the revenue recognition of IP licenses requires significant judgment and is discussed in further detail for each of the Company's license and collaboration agreements in Note 10, *Collaboration and license agreements*.

Milestone payments: At the inception of each arrangement that includes development or regulatory milestone payments, the Company evaluates the probability of reaching the milestones and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur in the future, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's, such as regulatory approvals, are not considered probable of being achieved until those approvals are received and therefore revenue recognized is constrained as management is unable to assert that a reversal of revenue would not be possible. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, the Company re-evaluates the probability of achievement of such development milestones and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment. To date, the Company has not recognized any milestone revenue resulting from any of its agreements.

Commercial Milestone Payments and Royalties: For arrangements that include sales-based royalties, including milestone payments based on levels of sales, if the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its agreements.

When no performance obligations are required of the Company, or following the completion of the performance obligation period, such amounts are recognized as revenue upon transfer of control of the goods or services to the customer. Generally, all amounts received or due other than sales-based milestones and royalties are classified as license and collaboration revenue. Sales-based milestones and royalties will be recognized as royalty revenue at the later of when the related sales occur or when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Deferred revenue expected to be recognized within the next twelve months is classified as a current liability.

#### ***Contract balances***

The Company recognizes a contract asset when the Company transfers goods or services to a customer before the customer pays consideration or before payment is due, excluding any amounts presented as an account or other receivable. A contract asset is an entity's right to consideration in exchange for goods or services that the entity has transferred to a customer. The contract liabilities, or deferred revenue, primarily relate to contracts where the Company has received payment, but it has not yet satisfied the related performance obligations. Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until the Company satisfies its obligations under these arrangements. Upfront payment contract liabilities resulting from the Company's license agreements do not represent a financing component as the payment is not financing the transfer of goods or services, and the technology underlying the licenses granted reflects research and development expenses already incurred by the Company. Deferred revenue expected to be recognized within the next twelve months is classified as a current liability

#### ***Research and development costs***

Research and development costs are charged to expense as incurred. Research and development costs consist of costs incurred in performing research and development activities, including salaries and bonuses, stock-based compensation, employee benefits, facilities costs, laboratory supplies, depreciation, manufacturing expenses, preclinical expenses, consulting, and other contracted services. The cost of obtaining licenses for certain technology or IP is recorded to research and development expense when incurred if the licensed technology or IP has not yet reached technological feasibility and has no alternative future use. Costs for certain research and development activities are recognized based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development costs.

#### ***Stock-based compensation***

The Company's stock-based compensation program allows for grants of stock options, restricted stock awards and restricted stock units. Grants are awarded to employees and non-employees, including directors.

The Company accounts for stock-based compensation in accordance with ASC Topic 718, *Compensation-Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees, non-employees and directors to be recognized as expense in the consolidated statements of operations and other comprehensive loss based on their fair values. The Company estimates the fair value of options granted using the Black-Scholes option pricing model, or Black-Scholes, for stock option grants to both employees and non-employees. The fair value of the Company's common stock is used to determine the fair value of restricted stock awards and restricted stock units.

Stock-based compensation awards are subject to either service- or performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees with performance-based vesting conditions is recognized based on grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the of performance condition is probable.

The Black-Scholes option pricing model requires inputs based on certain subjective assumptions, including (i) the expected stock price volatility, (ii) the expected term of the award, (iii) the risk-free interest rate, and (iv) expected dividends. Due to the lack of a public market for the Company's common stock prior to the IPO and continued lack of sufficient company-specific historical and implied volatility data, the Company has based its computation of expected volatility on the historical volatility of a representative group of public companies with similar characteristics to the Company, including stage of product development and life science industry focus. The historical volatility is calculated based on a period of time commensurate with expected term assumption. The Company uses the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share-Based Payment*, to calculate the expected term for options granted to employees and non-employees, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the options due to its lack of sufficient historical data. The risk-free interest rate is based on U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on its common stock. The Company recognizes forfeitures as they occur.

#### **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 in the accompanying consolidated statements of operations and other comprehensive loss.

#### **Variable interest entities**

The Company reviews each legal entity in which it has a financial interest to determine whether or not the entity is a variable interest entity, or VIE. If the entity is a VIE, the Company assesses whether or not it is the primary beneficiary of that VIE based on a number of factors, including (i) which party has the power to direct the activities that most significantly affect the VIE's economic performance, (ii) the parties' contractual rights and responsibilities pursuant to any contractual agreements and (iii) which party has the obligation to absorb losses or the right to receive benefits from the VIE. If the Company determines that it is the primary beneficiary of a VIE, it consolidates the financial statements of the VIE into its consolidated financial statements at the time that determination is made. On a quarterly basis, the Company evaluates whether it continues to be the primary beneficiary of any consolidated VIEs. If the Company determines that it is no longer the primary beneficiary of a consolidated VIE, or no longer has a variable interest in the VIE, the Company deconsolidates the VIE in the period that the determination is made.

#### **Income taxes**

The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the Company's financial statements and tax returns. Deferred tax assets and liabilities are determined based upon the differences between the financial statement carrying amounts and the tax bases of existing assets and liabilities and for loss and credit carryforwards, using enacted tax rates expected to be in effect in the year in which the differences are expected to reverse. Deferred tax assets are reduced by a valuation allowance if it is more likely than not that these assets may not be realized. The Company determines whether it is more likely than not that a tax position will be sustained upon examination. If it is not more likely than not that a position will be sustained, none of the benefit attributable to the position is recognized. The tax benefit to be recognized for any tax position that meets the more-likely-than-not recognition threshold is calculated as the largest amount that is more than 50% likely of being realized upon resolution of the contingency. The Company accounts for interest and penalties related to uncertain tax positions as part of its provision for income taxes.

#### **Comprehensive loss**

Comprehensive loss is defined as the change in stockholders' equity of a business enterprise during a period from transactions and other events and circumstances from non-owner sources. Comprehensive loss includes net loss as well as other changes in stockholders' deficit which includes certain changes in equity that are excluded from net loss. The Company's only element of other comprehensive loss is unrealized gains and losses on marketable securities.



### Net loss per share

The Company follows the two-class method when computing net loss per share, as the Company has issued shares that meet the definition of participating securities. The two-class method determines net 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 available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net loss per share attributable to common stockholders is computed by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net loss attributable to common stockholders is computed by adjusting net loss attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net loss per share attributable to common stockholders is computed by dividing the diluted net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of common stock equivalents.

For purposes of the dilutive net loss per share calculation, stock options and stock units for which the performance and market vesting conditions have been deemed probable, potential dilutive securities, which include redeemable convertible preferred stock, unvested restricted stock, and common stock options are considered to be common stock equivalents, while stock options and stock units with performance- or market-based vesting conditions that were not deemed probable are not considered to be common stock equivalents.

The Company's redeemable convertible preferred stock contractually entitled the holders of such shares to participate in dividends but did not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reported a net loss, such losses were not allocated to such participating securities. In periods in which the Company reported a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders was the same as basic net loss per share attributable to common stockholders, since dilutive common shares were not assumed to have been issued if their effect is anti-dilutive. The Company reported a net loss attributable to common stockholders for the years ended December 31, 2021, 2020 and 2019.

### Segment and geographic information

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

### 3. Property and equipment, net

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

	December 31,	
	2021	2020
Lab equipment	\$ 29,905	\$ 17,201
Leasehold improvements	57,760	12,706
Furniture and fixtures	3,679	1,078
Computer equipment	1,646	547
Construction in process	7,349	15,880
Total property and equipment	100,339	47,412
Less accumulated depreciation	(16,081)	(8,899)
Property and equipment, net	\$ 84,258	\$ 38,513

The following table summarizes depreciation expense incurred (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Depreciation expense	\$ 7,201	\$ 4,735	\$ 3,503

### 4. Fair Value of financial instruments

The Company's financial instruments that are measured at fair value on a recurring basis consist of cash equivalents, marketable securities, equity securities of Verve Therapeutics, Inc, or Verve, contingent consideration liabilities related to the Guide Merger Agreement and success payment derivative liabilities pursuant to the Harvard and Broad License Agreements.

The following tables set forth the fair value of the Company's financial assets and liabilities by level within the fair value hierarchy at December 31, 2021 (in thousands):

	Carrying amount	Fair value	Level 1	Level 2	Level 3
<b>Assets</b>					
Cash equivalents:					
Money market funds	\$ 540,094	\$ 540,094	\$ 540,094	\$ —	\$ —
Commercial paper	13,997	13,997	—	13,997	—
Corporate notes	5,903	5,903	—	5,903	—
Marketable securities:					
Commercial paper	368,743	368,743	—	368,743	—
Corporate notes	16,743	16,743	—	16,743	—
Equity securities included in marketable securities					
Corporate equity securities	20,167	20,167	20,167	—	—
<b>Total Assets</b>	<b>\$ 965,647</b>	<b>\$ 965,647</b>	<b>\$ 560,261</b>	<b>\$ 405,386</b>	<b>\$ —</b>
<b>Liabilities</b>					
Success payment liability – Harvard	21,000	21,000	—	—	21,000
Success payment liability – Broad Institute	21,200	21,200	—	—	21,200
Contingent consideration liability – Technology	24,359	24,359	—	—	24,359
Contingent consideration liability – Product	7,008	7,008	—	—	7,008
<b>Total liabilities</b>	<b>\$ 73,567</b>	<b>\$ 73,567</b>	<b>\$ —</b>	<b>\$ —</b>	<b>\$ 73,567</b>

The following tables set forth the fair value of the Company's financial assets and liabilities by level within the fair value hierarchy at December 31, 2020 (in thousands):

	Carrying amount	Fair value	Level 1	Level 2	Level 3
<b>Assets</b>					
Cash equivalents:					
Money market funds	\$ 88,259	\$ 88,259	\$ 88,259	\$ —	\$ —
Commercial paper	60,494	60,497	—	60,497	—
Corporate notes	12,314	12,308	—	12,308	—
Marketable securities:					
Commercial paper	113,622	113,622	—	113,622	—
Corporate notes	7,836	7,836	—	7,836	—
U.S. Treasury securities	11,009	11,009	—	11,009	—
Government securities	5,033	5,033	—	5,033	—
<b>Total Assets</b>	<b>\$ 298,567</b>	<b>\$ 298,564</b>	<b>\$ 88,259</b>	<b>\$ 210,305</b>	<b>\$ —</b>
<b>Liabilities</b>					
Success payment liability – Harvard	\$ 35,500	\$ 35,500	\$ —	\$ —	\$ 35,500
Success payment liability – Broad Institute	35,700	35,700	—	—	35,700
<b>Total liabilities</b>	<b>\$ 71,200</b>	<b>\$ 71,200</b>	<b>\$ —</b>	<b>\$ —</b>	<b>\$ 71,200</b>

**Cash equivalents** – Money market funds included within cash equivalents are classified within Level 1 of the fair value hierarchy because they are valued using quoted market prices in active markets. Commercial paper and corporate notes are classified within Level 2 of the fair value hierarchy because pricing inputs are other than quoted prices in active markets, which are either directly or indirectly observable as of the reporting date, and fair value is determined through the use of models or other valuation methodologies.

**Marketable securities** – Marketable securities, excluding corporate equity securities, are classified within Level 2 of the fair value hierarchy because pricing inputs are other than quoted prices in active markets, which are either directly or indirectly observable as of the reporting date, and fair value is determined using models or other valuation methodologies.

During the years ended December 31, 2021 and 2020, the Company held an investment in Verve consisting of shares of Verve's common and preferred stock. Prior to Verve's initial public offering in June 2021, the Company valued such investment based on the cost of the equity securities adjusted for any observable market transactions. Following the initial public offering, the equity securities have a readily determinable fair value; however, they were subject to transfer restrictions. As of December 31, 2021, the Company owned 546,970 shares of Verve's common stock, the value of which is included in marketable securities in the consolidated balance sheet as they are no longer subject to transfer restrictions. The Company recorded the investment at fair value of \$20.2 million as of December 31, 2021. In addition, the Company recorded other income of \$17.7 million and \$0.5 million for the years ended December 31, 2021 and 2020, respectively, related to the changes in fair value of Verve's common stock.

Pursuant to ASU No. 2016-01, *Recognition and Measurement of Financial Assets and Financial Liabilities*, the Company records changes in the fair value of its investments in equity securities to other income (expense), in the Company's consolidated statements of operations.

**Success Payment Liability** – As discussed further in Note 9, *License agreements*, the Company is required to make payments to Harvard and Broad Institute based upon the achievement of specified multiples of the initial weighted average value of the Company's Series A Preferred or, subsequent to the IPO, the market value of the Company's common stock, at specified valuation dates. The Company's liability for the share-based success payments under the Harvard and Broad License Agreements are carried at fair value. To determine the estimated fair value of the success payment liability, the Company uses a Monte Carlo simulation methodology, which models the future movement of stock prices based on several key variables.

The following variables were incorporated in the calculation of the estimated fair value of the Harvard and Broad Institute success payment liabilities:

	Harvard		Broad Institute	
	December 31, 2021	December 31, 2020	December 31, 2021	December 31, 2020
Fair value of common stock (per share)	79.69	81.64	79.69	81.64
Expected volatility	76 %	74 %	76 %	74 %
Expected term (years)	0.10-7.49	0.35-8.49	0.10-8.36	0.35-9.36

The computation of expected volatility was estimated using available information about the historical volatility of stocks of similar publicly traded companies for a period matching the expected term assumption. In addition, the Company incorporated the estimated number, timing, and probability of valuation measurement dates in the calculation of the success payment liability.

The following table reconciles the change in the fair value of success payment liabilities based on Level 3 inputs (in thousands):

	Harvard	Broad	Total
Balance at December 31, 2019	\$ 3,900	\$ 3,900	\$ 7,800
Change in fair value	31,600	31,800	63,400
Balance at December 31, 2020	\$ 35,500	\$ 35,700	\$ 71,200
Payments	\$ (15,000)	\$ (15,000)	\$ (30,000)
Change in fair value	500	500	1,000
Balance at December 31, 2021	\$ 21,000	\$ 21,200	\$ 42,200

**Contingent consideration liabilities** – As discussed further in Note 8, *Guide acquisition*, under the Guide Merger Agreement, Guide's former stockholders and optionholders are eligible to receive up to an additional \$100.0 million in technology milestone payments and \$220.0 million in product milestone payments, payable in the Company's common stock valued using the volume-weighted average price of the Company's stock over the ten-day trading period ending two trading days prior to the date on which the applicable milestone is achieved. As these milestones are payable in the Company's common stock, the milestone payments result in liability classification under ASC 480, *Distinguishing Liabilities from Equity*. These contingent consideration liabilities are carried at fair value which was estimated by applying a probability-based model, which utilized inputs based on timing of achievement that were unobservable in the market. These contingent consideration liabilities are classified within Level 3 of the fair value hierarchy.

The following table reconciles the change in fair value of the contingent consideration liabilities based on level 3 inputs (in thousands):

	For the Year Ended December 31, 2021		
	Technology Milestones	Product Milestones	Total
Balance at February 23, 2021 (inception)	\$ 29,403	\$ 7,110	\$ 36,513
Change in fair value	(5,044)	(102)	(5,146)
Balance at December 31, 2021	\$ 24,359	\$ 7,008	\$ 31,367

The following variables were incorporated in the calculation of the estimated fair value of the contingent consideration liabilities:

	<u>Technology Milestones</u> December 31, 2021	<u>Product Milestones</u> December 31, 2021
Discount Rate	7.50 %	7.50 %
Probability of Achievement	10-75%	2-15%
Projected Year of Achievement	2022-2023	2023-2029

## 5. Marketable securities

The following table summarizes the Company's marketable securities held at December 31, 2021 (in thousands):

	<u>Amortized Cost</u>	<u>Gross Unrealized Gains</u>	<u>Gross Unrealized Losses</u>	<u>Fair Value</u>
Commercial paper	\$ 368,778	\$ 32	\$ (67)	\$ 368,743
Corporate notes	16,758	—	(15)	16,743
Corporate equity securities	20,167	—	—	20,167
Total	<u>\$ 405,703</u>	<u>\$ 32</u>	<u>\$ (82)</u>	<u>\$ 405,653</u>

The following table summarizes the Company's marketable securities held at December 31, 2020 (in thousands):

	<u>Amortized Cost</u>	<u>Gross Unrealized Gains</u>	<u>Gross Unrealized Losses</u>	<u>Fair Value</u>
Commercial paper	\$ 113,628	\$ 11	\$ (17)	\$ 113,622
Corporate notes	7,839	2	(5)	7,836
U.S. Treasury securities	11,009	—	—	11,009
Government securities	5,033	—	—	5,033
Total	<u>\$ 137,509</u>	<u>\$ 13</u>	<u>\$ (22)</u>	<u>\$ 137,500</u>

The amortized cost of marketable securities is adjusted for amortization of premiums and accretion of discounts to maturity. At December 31, 2021, the balance in accumulated other comprehensive (loss) income was comprised solely of activity related to marketable securities. There were no realized gains or losses recognized on the sale or maturity of marketable securities for the years ended December 31, 2021, 2020 and 2019 and, as a result, the Company did not reclassify any amounts out of accumulated other comprehensive (loss) income for the same periods.

The Company holds debt securities of companies with high credit quality and has determined that there was no material change in the credit risk of any of its debt securities. The contractual maturity dates of all the investments are less than one year.

## 6. Accrued expenses and other current liabilities

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

	<u>December 31,</u>	
	<u>2021</u>	<u>2020</u>
Employee compensation and related benefits	11,661	7,591
Process development and manufacturing costs	3,833	2,272
Professional fees	3,330	1,948
Research costs	3,133	2,423
Other	6,964	4,229
Total	<u>\$ 28,921</u>	<u>\$ 18,463</u>

## 7. Leases

### Operating leases

The Company's operating leases are as follows:

- A February 2018 lease for 38,203 square feet of office and laboratory space, which commenced in March 2018 and terminates in September 2028. The lease is subject to fixed-rate rent escalations and provided for \$6.1 million in tenant improvements and a term extension option, which is not reasonably certain of exercise.

- An October 2018 lease for laboratory space, which commenced in April 2019 and was amended in March 2020, April 2020, January 2021 and October 2021. The lease, as amended, commenced in April 2020 and terminates in December 2025. The amended lease is subject to fixed-rate rent escalations and provided an option to extend the lease for two additional two-year periods through December 31, 2029, which are not reasonably certain of being exercised. Upon commencement of the March 2020 amendment, the Company recorded an ROU asset and a lease liability of \$4.2 million. Upon commencement of the April 2020 amendment, the Company recorded an operating lease ROU asset and a lease liability of \$1.8 million. This lease was amended to add additional space in January and October of 2021. The Company recorded an operating lease ROU asset and a lease liability of \$0.3 million in January 2021 related to the January 2021 amendment and an operating lease ROU asset and lease liability of \$1.6 million in October 2021 related to the October 2021 amendment.
- Leases in June 2019 and July 2019 for office and laboratory space, both of which commenced in October 2019 and terminated in December 2021.
- An April 2019 lease for office and laboratory space that was built over the course of 2020 and 2021. Pursuant to the terms of the original lease agreement, the first phase of the lease commenced in October 2020 (rent payments for the first phase began in August 2021) and the second phase of the lease commenced in January 2021 (rent payments for the second phase began in February 2022). The lease is subject to fixed-rate rent escalations and provides for \$23.4 million in tenant improvements and the option to extend the lease for two terms of five years each, which are not reasonably certain of exercise. The Company determined that it is the accounting owner of all tenant improvements. The Company maintains a security deposit of \$9.7 and \$11.8 million in the form of a letter of credit, which is included in restricted cash as of December 31, 2021 and 2020, respectively. Upon commencement of the first phase of this lease in October 2020, the Company recorded an operating lease ROU asset of \$66.8 million and a lease liability of \$68.8 million and upon commencement of the second phase of this lease in January 2021, the Company recorded an operating lease ROU asset of \$22.0 million and a corresponding lease liability of \$23.0 million. Subsequently, during the second quarter of 2021, the Company amended the rent commencement dates of the first and second phases of this lease. Pursuant to the terms of the amendment, the lease will terminate in February 2034, which is 12 years from the amended second phase rent commencement date. As a result, the Company recorded an increase in the ROU asset of \$0.5 million and lease liability of \$0.5 million.

The Company identified and assessed the following estimates in recognizing the operating lease right-of-use asset and corresponding liability:

- Expected lease term: The expected lease term includes noncancelable lease periods and, when applicable, periods covered by an option to extend the lease if the Company is reasonably certain to exercise that option, as well as periods covered by an option to terminate the lease if the Company is reasonably certain not to exercise that option.
- Incremental borrowing rate: As the discount rates in the Company's lease are not implicit, management estimated the incremental borrowing rate based on the rate of interest the Company would have to pay to borrow a similar amount on a collateralized basis over a similar term.
- Lease and non-lease components: The Company is required to pay fees for operating expenses in addition to monthly base rent for certain operating leases (non-lease components). The Company has elected the practical expedient which allows non-lease components to be combined with lease components for all asset classes. Variable non-lease components are not included within the lease right-of-use asset and lease liability on the consolidated balance sheet, and instead are reflected as expense in the period they are paid.

The following table summarizes operating lease costs as well as sublease income (in thousands):

	December 31,		
	2021	2020	2019
Operating lease costs	\$ 18,309	\$ 8,415	\$ 4,078
Variable lease costs	2,065	929	811
Short-term lease costs	1,145	—	116
Sublease income	(110)	—	(51)
Total	<u>\$ 21,409</u>	<u>\$ 9,344</u>	<u>\$ 4,954</u>

The following table summarizes the lease term and discount rate for operating leases:

	December 31,	
	2021	2020
Weighted-average remaining lease term (years)	11.1 years	11.5 years
Weighted-average discount rate	7.0 %	7.4 %

The following table summarizes the lease costs included in the measurement of lease liabilities (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Operating cash flows used for operating leases	\$ 11,462	\$ 6,911	\$ 4,950
Operating lease liabilities arising from obtaining ROU assets	25,925	74,723	6,221

At December 31, 2021, the future minimum lease payments for the Company's operating leases for each of the next five years and total thereafter were as follows (in thousands):

2022	17,059
2023	17,733
2024	18,269
2025	18,703
2026	17,143
Thereafter	115,692
<b>Total undiscounted lease payments</b>	<b>204,599</b>
Less: imputed interest	(62,249)
<b>Total operating lease liabilities</b>	<b>\$ 142,350</b>

In August 2020, the Company entered into a lease agreement with Alexandria Real Estate Equities, Inc., or the Landlord, to build a 100,000 square foot manufacturing facility in Research Triangle Park, North Carolina, intended to support a broad range of clinical programs. The lease has a term of 15 years following the commencement date and provides the Company the option to extend the lease term for two five-year terms. It is subject to fixed rate escalation increases and also provides up to \$20.0 million for reimbursement of tenant improvements. As the lease had not commenced as of December 31, 2021, the Company has not recorded an operating lease ROU asset or lease liability for this lease in the consolidated balance sheets. The lease payments are subject to adjustment following the determination of the total project costs of the landlord. The initial estimate of the minimum amount of undiscounted lease payments due under this lease is \$69.0 million. The Company anticipates that the facility will be operational in the first quarter of 2023 and that is when it will begin making rent payments. The tabular disclosure of minimum lease payments above does not include payments due under this lease.

In August 2021, the Company executed a lease amendment to its April 2019 lease for office and laboratory space in Cambridge, Massachusetts to occupy additional space. The term of this lease will run concurrent with the term of the April 2019 lease. The initial estimate of the minimum amount of undiscounted lease payments due under this lease is \$11.1 million. As the lease had not yet commenced as of December 31, 2021, the Company has not recorded an operating lease ROU asset or lease liability for this lease in the consolidated balance sheets. The tabular disclosure of minimum lease payments above does not include payments due under this lease.

In October 2021, the Company executed a lease for additional office and laboratory space at an existing facility. The term of this lease will run through December 31, 2025. As part of this lease, the Company took access to the remainder of this space in January 2022 and will record an operating lease ROU asset and lease liability during the first quarter of 2022. The initial estimate of the minimum amount of undiscounted lease payments due under this lease is \$2.6 million. Additionally, in February 2022, the Company executed a lease for additional office and laboratory space at this facility with a lease term to run through December 31, 2025. The Company took access to this space in February 2022 and will record an operating lease ROU asset and lease liability during the first quarter of 2022. The initial estimate of the minimum amount of undiscounted lease payments due under this lease is \$3.1 million. The tabular disclosure of minimum lease payments above does not include the payments under this segment of the lease.

#### **Financing obligations**

In July 2019, the Company sold certain equipment to a leasing company for a total of \$3.8 million, and, concurrently, entered into a lease agreement with the leasing company to lease back the equipment for an annual rent of \$1.0 million over a term of four years.

In October 2019, the Company sold additional equipment to the leasing company for a total of \$2.4 million and, concurrently, entered into a lease agreement with the leasing company to lease back the equipment for an annual rent of \$0.7 million over a term of four years.

In February 2020, the Company sold additional equipment to the leasing company for a total of \$1.6 million and, concurrently, entered into a lease agreement with the leasing company to lease back the equipment for an annual rent of \$0.5 million over a term of four years.

In December 2020, the Company sold additional equipment to the leasing company for a total of \$1.6 million and, concurrently, entered into a lease agreement with the leasing company to lease back the equipment for an annual rent of \$0.5 million over a term of four years.

The equipment leases are being accounted for as financings as the lease terms are for substantially all the remaining economic life of the underlying equipment. The Company concluded that control, including the significant risks and rewards of ownership, did not effectively transfer to the buyer-lessor at the inception of the sale and leaseback transactions. As a result, the transactions are accounted for as failed sale and leasebacks and result in the recognition of financing liabilities.

The future minimum payments related to the equipment financing obligations for each of the next five years were as follows (in thousands):

Years ending December 31,	Amount
2022	2,663
2023	2,013
2024	511
2025	—
2026	—
Total	5,187
Less: amounts representing interest at 8.76%	(568)
Plus: residual values	675
Financing obligations	<u>\$ 5,294</u>

The following table summarizes the breakdown of the principal and interest portions of the equipment financing payments (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Paydown of principal	\$ 2,118	\$ 1,569	\$ 464
Payment of interest	567	561	187

## 8. Guide acquisition

On February 23, 2021, the Company entered into the Guide Merger Agreement. Under the Guide Merger Agreement, the Company paid Guide's former stockholders and optionholders upfront consideration in an aggregate amount of \$120.0 million, excluding customary purchase price adjustments and closing costs, in shares of the Company's common stock, based upon the volume-weighted average price of the Company's stock over the ten trading-day period ending on February 19, 2021. Pursuant to the Guide Merger Agreement, the Company acquired all of the issued and outstanding shares of Guide. The Company issued a total of 1,087,153 shares of its common stock valued at \$120.0 million in connection with the upfront payment to Guide's former stockholders and optionholders. The Guide transaction resulted in the acquisition of certain know-how and intellectual property assets related to Guide's proprietary *in vivo* LNP screening technology and its library of lipids and lipid nanoparticle formulations identified using the screening technology. Management determined that the acquired assets do not meet the definition of a business pursuant to ASC 805, *Business Combinations*, as substantially all of the fair value of the acquired assets is concentrated into one identifiable asset, the LNP screening technology and associated lipid library. As of the date of closing of the transactions contemplated by the Guide Merger Agreement, or the Guide Merger Agreement Date, the asset acquired had no alternative future use and had not reached a stage of technological feasibility. As a result, all share-based and cash payment obligations have been recorded as research and development expense in the consolidated statements of operations and other comprehensive loss in the amount of \$155.0 million. The total transaction price was allocated to the assets acquired and liabilities assumed on a relative fair value basis.

In addition, Guide's former stockholders and optionholders are eligible to receive up to an additional \$100.0 million in technology milestone payments and \$220.0 million in product milestone payments, payable in the Company's common stock valued using the volume-weighted average price of the Company's stock over the ten trading-day period ending two trading days prior to the date on which the applicable milestone is received.

The Company determined that all future technology and product milestone payments are classified as contingent consideration liabilities under ASC 480 and therefore the Company recorded a liability for these milestone payments as of the Guide Merger Agreement Date at fair value of \$36.5 million. These contingent consideration liabilities are remeasured at fair value each financial reporting period, with the resulting impact reflected in the Company's consolidated statements of operations and other comprehensive loss, presented within other income (expense).

The transaction price was determined and allocated as follows (in thousands):

<b>Transaction price</b>		
Fair value of equity instruments issued	\$	120,032
Technology and product contingent consideration liabilities		36,513
Transaction costs		2,531
<b>Total transaction price</b>	<b>\$</b>	<b>159,076</b>
<b>Transaction price allocated</b>		
In-process research and development	\$	154,953
Cash acquired		3,151
Prepaid expenses and other assets		264
Property and equipment		1,835
Assembled workforce		300
Other liabilities assumed		(1,427)
<b>Total transaction price</b>	<b>\$</b>	<b>159,076</b>

## 9. License agreements

### *Harvard license agreement*

In June 2017, the Company entered into the Harvard License Agreement for certain base editing technology pursuant to which the Company received an exclusive, worldwide, sublicensable, royalty-bearing license under specified patent rights to develop and commercialize licensed products and a nonexclusive, worldwide, sublicensable, royalty-bearing license under certain patent rights to research and develop licensed products. The Company agreed to use commercially reasonable efforts to develop licensed products in accordance with the development plan, to introduce any licensed products that gain regulatory approval into the commercial market, to market licensed products that have gained regulatory approval following such introduction into the market, and to make licensed products that have gained regulatory approval reasonably available to the public. The license term extends until the later of the expiration of (i) the last to expire licensed patent covering a licensed product, (ii) the period of exclusivity associated with a licensed product or (iii) a certain period after the first commercial sale of a licensed product, unless terminated earlier by either party under certain provisions.

As partial consideration for the rights granted under the Harvard License Agreement, the Company issued to Harvard 101,363 shares of the Company's common stock. Additional consideration under the Harvard License Agreement included an Anti-Dilution Issuance Right, which was settled during the year ended December 31, 2018, Financing Milestone Payments related to Series A Preferred and Series B Preferred financings, which were paid and settled in the year ended December 31, 2019, and Success Payments, which are further described below. The Anti-Dilution Issuance Right and Financing Milestone Payments related to Series A Preferred and Series B Preferred financings were both expensed in the year 2018 and prior.

**Success Payments** – Under the Harvard License Agreement, Harvard is entitled to receive success payments, in cash or shares of Company stock, determined based upon the achievement of specified multiples of the initial weighted average value of the Company's Series A Preferred at specified valuation dates. The success payments range from \$5.0 million to a maximum of \$105.0 million and have valuation multiples that range from 5 times to 40 times the initial weighted average value of the Series A Preferred. Subsequent to the Company's February 2020 IPO, the amount of success payments is based on the market value of the Company's common stock.

The Company is required to make success payments to Harvard during a period of time, or the Harvard Success Payment Period, which has been determined to be the later of (1) the ninth anniversary of the Harvard License Agreement or (2) the earlier of (a) the twelfth anniversary of the Harvard License Agreement and (b) the third anniversary of the first date on which a licensed product receives regulatory approval in the United States. During the Harvard Success Payment Period, the Company will perform a calculation of any amounts owed to Harvard on each rolling 90-day period, commencing one year after the Company's IPO.

In May 2021, the first success payment measurement occurred and amounts due to Harvard were calculated to be \$15.0 million. The Company elected to make the payment in shares of the Company's common stock and issued 174,825 shares of the Company's common stock to settle this liability on June 10, 2021. The Company may owe Harvard success payments of up to an additional \$90.0 million.

The following table summarizes the Company's success payment liability for Harvard (in thousands):

	December 31,	
	2021	2020
Harvard success payment liability	\$ 21,000	\$ 35,500



The following table summarizes the expense resulting from the change in the fair value of the success payment liability for Harvard (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Change in fair value of Harvard success payment liability	\$ 500	\$ 31,600	\$ 2,700

**Other Payments** – The Company agreed to pay Harvard an annual license maintenance fee ranging from low-to-mid five figures to low six figures, depending on the calendar year. The Company is responsible for the payment of certain patent prosecution and maintenance costs incurred by Harvard related to licensed patents. To the extent achieved, the Company is obligated to pay up to an aggregate of \$75.9 million in product development and regulatory approval milestones, or Harvard Product Milestones. If the Company completes a change of control during the term of the Harvard License Agreement, then certain of the milestone payments would be increased. To the extent there are sales of a licensed product, the Company is required to pay low single digit royalties on net sales. The Company is entitled to certain reductions and offsets on these royalties with respect to a licensed product in a given country. If the Company sublicenses its rights to develop or commercialize a licensed product under the Harvard License Agreement to a third party and the Company receives non-royalty sublicense income, then Harvard is entitled to a percentage of such consideration, ranging from the high single digits to low double digits depending on the date in which such sublicense agreement is executed and the stage of development of the Company's licensed products at such time.

The annual maintenance fees will be recorded as an expense on an annual basis based on the stated amount for the applicable year. Annual patent costs will be expensed as incurred. Upon determination that a Harvard Product Milestone is probable to occur, the amount due will be recorded as research and development expense. The Company will monitor the Harvard Product Milestone payments for this arrangement on an ongoing basis. In November 2021, the Company triggered a regulatory milestone owed under this agreement and recorded expense of \$0.1 million for the year ended December 31, 2021. No expense was recorded for these milestones for the years ended December 31, 2020 and 2019. Lastly, to the extent products are commercialized under the Harvard License Agreement, the Company will accrue royalty expense and sublicense nonroyalty payments, as applicable, for the amount it is obligated to pay, with adjustments as sales are made. The Company has incurred \$33.7 million of expense related to non-royalty sublicense fees owed to Harvard for the twelve months ended December 31, 2021.

#### **Broad license agreement**

In May 2018, the Broad License Agreement was entered into with Broad Institute for certain RNA base editing technology including an RNA editor platform. Under the Broad License Agreement, Broad Institute granted exclusive and non-exclusive worldwide, sublicensable, royalty-bearing licenses under specified patent rights to develop and commercialize licensed product and a nonexclusive, worldwide, sublicensable, royalty-bearing license under certain patent rights to research and develop licensed products. Under the agreement the Company shall use commercially reasonable efforts to develop licensed products in accordance with the development plan, to introduce any licensed products that gain regulatory approval into the commercial market, to market licensed products that have gained regulatory approval following such introduction into the market, and to make licensed products that have gained regulatory approval reasonably available to the public. The license term extends until the later of the expiration of (i) the last to expire licensed patent covering a licensed product, (ii) the period of regulatory exclusivity associated with a licensed product or (iii) a certain period after the first commercial sale of a licensed product unless terminated earlier by either party under certain provisions.

Additional consideration under the Broad License Agreement included an Anti-Dilution Issuance Right, which was paid and settled during the year ended December 31, 2018, Financing Milestone Payments related to Series A Preferred and Series B Preferred financings, which were settled in the year ended December 31, 2019, and Success Payments, which are further described below. The Anti-Dilution Issuance Right and Financing Milestone Payments related to Series A Preferred and Series B Preferred financings were both expensed in the year 2018.

**Success Payments** – Under the Broad License Agreement, Broad Institute is entitled to receive success payments, in cash or shares of Company common stock, determined based upon the achievement of specified multiples of the initial weighted average value of the Series A Preferred at specified valuation dates. The success payments range from \$5.0 million to a maximum of \$105.0 million and have valuation multiples that range from 5 times to 40 times the initial weighted average value of the Series A Preferred. Subsequent to the February 2020 IPO, the amount of success payments is based on the market value of the Company's common stock. The Company is required to make success payments to Broad Institute during a period of time, or the Broad Success Payment Period, which has been determined to be the earliest of (1) the twelfth anniversary of the Broad License Agreement or (2) the third anniversary of the first date on which a licensed product receives regulatory approval in the United States. During the Broad Success Payment Period, the Company will perform a calculation of any amounts owed to Broad Institute on each rolling 90-day period, commencing one year after the Company's IPO.

In May 2021, the first success payment measurement occurred and amounts due to Broad Institute were calculated to be \$15.0 million. The Company elected to make the payment in shares of the Company's common stock and issued 174,825 shares of the Company's common stock to settle this liability on June 10, 2021. The Company may owe Broad Institute success payments of up to an additional \$90.0 million.

The following table summarizes the Company's success payment liability for Broad Institute (in thousands):

	December 31,	
	2021	2020
Broad Institute success payment liability	\$ 21,200	\$ 35,700

The following table summarizes the expense resulting from the change in the fair value of the success payment liability for Broad Institute (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Change in fair value of Broad Institute success payment liability	\$ 500	\$ 31,800	\$ 2,700

**Other Payments** – The Company agreed to pay Broad Institute an annual license maintenance fee ranging from low-to-mid five figures to low six figures, depending on the particular calendar year. The Company is responsible for the payment of certain patent prosecution and maintenance costs incurred by Broad Institute related to licensed patents. To the extent achieved, the Company is obligated to pay up to an aggregate of \$75.9 million in product development and regulatory approval milestones, or Broad Product Milestones. If the Company completes a change of control during the term of the Broad License Agreement, then certain of the milestone payments would be increased. To the extent there are commercial sales of a licensed product, the Company is required to pay low single digit royalties on net sales. The Company is entitled to certain reductions and offsets on these royalties with respect to a licensed product in a given country. If the Company sublicenses its rights to develop or commercialize a licensed product under the Broad License Agreement to a third party and the Company receives non-royalty sublicense income, then Broad Institute is entitled to a percentage of such consideration, ranging from the high single digits to low double digits depending on the date in which such sublicense agreement is executed and the stage of development of the Company's licensed products at such time.

The annual maintenance fees will be recorded as an expense on an annual basis based on the stated amount for the applicable year. Annual patent costs will be expensed as incurred. Upon determination that a Broad Product Milestone is probable to occur, the amount due will be recorded as research and development expense. The Company will monitor the Broad Product Milestone payments for this arrangement on an ongoing basis. The triggering of these milestone payments was not considered probable as of the acquisition date, and no expense has been recorded for these milestones during the years ended December 31, 2021, 2020 and 2019. Lastly, to the extent products are commercialized under the Broad License Agreement, the Company will accrue royalty expense and sublicense nonroyalty payments, as applicable, for the amount it is obligated to pay, with adjustments as sales are made. The Company has incurred \$6.1 million of expense related to non-royalty sublicense fees owed to Broad Institute for the twelve months ended December 31, 2021.

#### ***Editas license agreement***

In May 2018, the Company entered into a license agreement, or the Editas License Agreement, with Editas Medicine, Inc., or Editas. Pursuant to the Editas License Agreement, Editas granted to the Company licenses and options to acquire licenses to certain intellectual property rights owned or controlled by Editas, for specified uses. More specifically, Editas granted to the Company a worldwide, exclusive, sublicensable, license (subject to certain exceptions and conditions) under certain intellectual property controlled by Editas for the use of base editing therapies for the treatment of any field of human diseases and conditions, subject to certain exceptions, or the Beam Field, and the licenses granted or to be granted under the Editas License Agreement, or the Editas Development and Commercialization License. Additionally, Editas granted to the Company a royalty-free, non-exclusive license under certain intellectual property owned or controlled by Editas to perform research activities in the Beam Field, or the Editas Research License. Editas provided the Company with an exclusive option to obtain an Editas Development and Commercialization License to three additional groups of intellectual property owned or controlled by Editas, on a group by group basis, during the specified option period, subject to certain exceptions. Pursuant to the Editas License Agreement, the Company will use commercially reasonable efforts to develop a product that includes the rights licensed to the Company within a specified period of time and to commercialize any such products that have received regulatory approval in certain specified countries.

Additional consideration will be due to Editas if the Company elects to exercise its option to obtain an Editas Development and Commercialization License to any of the three categories of intellectual property underlying the Editas Research License, for a fee ranging from a mid-teen million dollar amount to a low to mid-eight digit dollar amount per group, depending on the timing of the option exercise. Additionally, the Company is required to reimburse Editas for certain payments Editas may be obligated to make under existing Editas license agreements related to the intellectual property being licensed to the Company, including (i) development, regulatory and commercial milestone payments and certain sublicense income payments due as a result of the Editas License Agreement and (ii) a percentage of the annual maintenance fees and patent fees due to certain of the Editas' licensors. In addition, to the extent any products are commercialized under an Editas Development and Commercialization License, the Company would be required to make royalty payments equivalent to the royalties that would be due from Editas to any applicable licensors of Editas related to the sales of such licensed products, plus an additional tiered low- to mid-single digit royalty, depending on whether such licensed product is covered by an Editas-owned patent.

The license rights and option rights granted by Editas to the Company are subject to the terms and conditions of the underlying license agreements that Editas is a party to and under which Editas licensed rights or option rights to the Company and the termination of such in-licenses, as applicable. Unless earlier terminated by either party pursuant to the terms of the agreement, the Editas License Agreement will continue in full force and effect and will expire on a licensed product-by-licensed product and country-by-country basis upon the later of (i) the last-to-expire royalty term under any applicable institutional license to Editas and (ii) the date at which such product is no longer covered by a valid claim of a licensed Editas-owned patent in such country. The Company has the right, at its sole discretion, at any time to terminate the Editas License Agreement in its entirety or on a group-by-group of intellectual property basis, upon ninety days written notice to Editas. Upon termination of the Editas License Agreement, all rights and licenses granted by Editas to the Company (including the rights to exercise options and obtain such licenses) will immediately terminate and patents within a group of patents will no longer be deemed licensed patents. Expiration or termination of the Editas License Agreement for any reason does not release either party of any obligation or liability which had accrued, or which is attributable to a period prior to such expiration or termination.

The option exercise fees under the agreement will be recorded as research and development expense, if and when the Company exercises such options. To date, no options have been exercised. The annual maintenance fees are recorded as an expense on an annual basis based on the stated amount for the applicable year. Annual patent costs are expensed as incurred. In addition, the Company is required to make certain development, regulatory and commercial milestone payments to Editas upon the achievement of specified milestones. During the twelve months ended December 31, 2021, the Company recognized \$0.1 million of expense as it determined that it owed a regulatory milestone payment to Editas under the License Agreement. No expense has been recorded for these milestones during the years ended December 31, 2020 and 2019. To the extent applicable, sublicense income payments will be accrued for the amount the Company is obligated to pay under each applicable in-license as amounts are due to Editas. Lastly, to the extent products are commercialized under the Editas License agreement, the Company will accrue royalty expense for the amount it is obligated to pay, with adjustments as sales are made.

#### ***Bio Palette license agreement***

In March 2019, the Company entered into a license agreement with Bio Palette pursuant to which the Company received an exclusive (even as to Bio Palette), sublicensable license under certain patent rights related to base editing owned or controlled by Bio Palette to exploit products for the treatment of human disease throughout the world, but excluding products in the microbiome field in Asia (the "Bio Palette License Agreement"). In addition, the Company granted Bio Palette an exclusive (even as to the Company) license under certain patent rights related to base editing and gene editing owned or controlled by the Company to exploit products in the microbiome field in Asia. Each party to the agreement retains non-exclusive rights to develop and manufacture products in the microbiome field worldwide for the sole purpose of exploiting those products in its own territory. Each party agrees to certain coordination obligations in the microbiome field if either party determines not to exploit their rights in such field. Unless earlier terminated, the Bio Palette License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of the applicable royalty term for each such licensed product and country. To the extent products are commercialized under the Bio Palette License Agreement, the Company will accrue royalty expense for the amount it is obligated to pay, with adjustments as sales are made.

The Company also agreed to pay a royalty at a fraction of a percent on net sales of products that are covered by the patents licensed by Bio Palette to the Company, and Bio Palette agreed to pay a royalty at a fraction of a percent on net sales of products that are covered by the patents licensed by the Company to Bio Palette. The royalty term for a product in a country will terminate on the later of the expiration of (i) patent-based exclusivity with respect to such licensed product in such country or (ii) regulatory exclusivity with respect to such licensed product in such country.

Upon the execution of the Bio Palette License Agreement, the Company paid Bio Palette an upfront fee of \$0.5 million and issued to Bio Palette 16,725 shares of its common stock valued at \$0.1 million, which were recorded as research and development expense for the year ended December 31, 2019. Upon the issuance of a certain Bio Palette patent in the United States in June 2020, the Company made a milestone payment of \$2.0 million and, in July 2020, issued to Bio Palette 175,000 shares of its common stock valued at \$0.3 million, which were recognized as research and development expense. The fair value of the common stock issued to Bio Palette under the Bio Palette License Agreement was measured at the inception of arrangement and expensed when the issuance of shares became probable.

Management concluded that the licenses acquired from each transaction above did not meet the accounting definition of a business as inputs, but no processes or outputs were acquired with the licenses, and the licensed technology had not achieved technological feasibility. As the inputs that were acquired along with the licenses do not constitute a “business,” the transactions have been accounted as asset acquisitions. As of the date of each License Agreement, the assets acquired had no alternative future use and the assets had not reached a stage of technological feasibility. As a result, all share-based and cash payment obligations have been recorded as research and development expense in the accompanying consolidated statements of operations and other comprehensive loss.

## 10. Collaboration and license agreements

### *Pfizer*

In December 2021, the Company entered into a research collaboration agreement, or the Pfizer Agreement, with Pfizer Inc., or Pfizer, focused on the use of certain of the Company’s base editing technology to develop *in vivo* therapies for rare genetic diseases of the liver, muscle, and central nervous system. Under the terms of the Pfizer Agreement, the Company will apply certain of its base editing technology and conduct all research activities through development candidate selection for three base editing programs that target specific genes corresponding to specific diseases that are the subject of such programs. Pfizer will have exclusive rights to license each of the three programs at no additional cost, each an Opt-In Right, and will assume responsibility for subsequent development and commercialization. At the end of the Phase 1/2 studies, the Company may elect to enter into a global co-development and co-commercialization agreement with Pfizer with respect to one program licensed under the collaboration for an option exercise fee equal to a percentage of the applicable development costs incurred by Pfizer, or the Participation Election. In the event the Company elects to exercise its Participation Election, upon the payment of its option exercise fee, Pfizer and the Company would share net profits as well as development and commercialization costs in a 65%/35% (Pfizer/Company) split for such program. The research collaboration will be managed on an overall basis by a Joint Research Committee, or JRC, formed by an equal number of representatives from the Company and Pfizer.

At the inception of the Pfizer Agreement, the Company is entitled to receive a nonrefundable upfront payment of \$300.0 million in consideration for the rights granted to Pfizer under the collaboration. Should Pfizer exercise its Opt-In Right for any of the three programs, the Company would be eligible to receive development, regulatory, and commercial milestones of up to \$350.0 million per program, for a potential total consideration of up to \$1.35 billion, plus royalty payments on global net sales for each licensed program. If Pfizer does not exercise its Opt-In Right for a program, the Company’s rights in such program revert to the Company and the Company will be required to pay Pfizer earn-out payments equal to a low single digit percentage of net sales earned on such program for a ten-year period. As the \$300.0 million upfront fee was not received by the Company as of December 31, 2021, the Company recorded a collaboration receivable for \$300.0 million with a corresponding deferred revenue liability. The Company received the \$300.0 million in January 2022.

During the collaboration term, Pfizer has a one-time option to substitute a disease that is the subject of a specific program with one pre-defined substitute disease. The collaboration has an initial term of four years and may be extended for an additional one year on a program-by-program basis. Pfizer may terminate the Pfizer Agreement for convenience on any or all of the programs by providing 90 days’ prior written notice.

The Company accounts for the Pfizer Agreement under ASC 606, *Revenue from Contracts with Customers*, or ASC 606, as it includes a customer-vendor relationship as defined under ASC 606 and meets the criteria to be considered a contract.

The overall transaction price as of the inception of the contract was determined to be \$300.0 million, which is comprised entirely of the nonrefundable upfront payment. There is no variable consideration included in the transaction price at inception as the future milestone payments are fully constrained and the Company is not required to estimate variable consideration for the royalty payments at contract inception. The Company will re-evaluate the transaction price in each reporting period.

The Company has concluded that the licenses to its base editing technology, including the exclusive development and commercialization rights, are not capable of being distinct from the other performance obligations, and as such the Company has determined that the licenses combined with the other research and development services represent performance obligations and no up-front revenue was recognized for the licenses. The Company plans to recognize revenue for each performance obligation as it is satisfied over time using an input method. As no activities under the Pfizer Agreement had commenced as of December 31, 2021, the entire \$300.0 million is recorded as deferred revenue and no revenue was recognized for the twelve months ended December 31, 2021. Based on the current estimated timelines, the deferred revenue is expected to be recognized as revenue over approximately four years from December 31, 2021.

### ***Sana Biotechnology***

In October 2021, the Company entered into an option and license agreement, or the Sana Agreement, with Sana Biotechnology, Inc., or Sana, under which the Company granted Sana a license for non-exclusive rights to its CRISPR Cas12b nuclease system for the development and commercialization of certain engineered cellular therapy programs. In addition to the license, the Company performed an initial technology transfer following the effective date of the Sana Agreement providing Sana with certain know-how, as required under the Sana Agreement. This technology transfer occurred in 2021. Following the license transfer and completion of the initial technology transfer, Sana is responsible, at its sole expense, for the development and commercialization of therapeutic products which must contain either specified CAR antigen targets or pluripotent stem cell, or PSC, product types.

As consideration for the license, the Company received an upfront payment of \$50.0 million from Sana in October 2021. In addition, the Company may be eligible to receive development, regulatory, and commercial milestones of up to \$65.0 million from Sana on any product candidate or product. The Company will also be entitled to receive royalties equal to a low single digit percentage of net sales on any product.

For up to one year following the effective date of the Sana Agreement, Sana has the option to select up to a cumulative total of two additional CAR antigen targets or PSC product types for an additional fee of \$10.0 million per additional CAR antigen target and additional PSC product type, or the Option Rights, for an aggregate potential additional consideration of \$20.0 million. Further, at any time prior to the third anniversary of the effective date of the Sana Agreement, Sana has a one-time right to substitute, in the aggregate, either one CAR antigen target or one PSC product type at no additional cost, or the Replacement Right. Sana may also select a specified number of additional or replacement genetic targets for each PSC product type at any time prior to the third anniversary of the effective date at no additional cost, or the Genetic Target Nomination Rights. Sana may terminate the Sana Agreement for convenience prior to the first commercial sale of any licensed product by providing 90 days' prior written notice or upon 180 days' prior written notice after first commercial sale.

The Company accounts for the Sana Agreement under ASC 606 as it includes a customer-vendor relationship as defined under ASC 606 and meets the criteria to be considered a contract. The overall transaction price as of the inception of the contract was determined to be \$50.0 million, which is composed entirely of the nonrefundable upfront payment. There is no variable consideration included in the transaction price at inception as the future milestone payments are fully constrained and the Company is not required to estimate variable consideration for the royalty payments at contract inception. The Company will re-evaluate the transaction price in each reporting period.

The Company has identified a single performance obligation, which includes (i) the non-exclusive license granted to Sana under the Company's patent rights and know-how and (ii) the initial technology transfer following the effective date, which occurred in 2021. The Company further concluded that the Option Rights, Replacement Right, and Genetic Target Nomination Rights did not grant Sana a material right. As the Company only identified one performance obligation, no allocation of the transaction price is required.

The Company recognized revenue for the performance obligation at a point in time upon the transfer of the license to Sana and completion of the initial technology transfer, which occurred in October 2021. For the twelve-month period ended December 31, 2021, the Company has recognized \$50.0 million of revenue under the Sana Agreement.

### ***Apellis Pharmaceuticals***

In June 2021, the Company entered into a research collaboration agreement, or the Apellis Agreement, with Apellis Pharmaceuticals, Inc., or Apellis, focused on the use of certain of the Company's base editing technology to discover new treatments for complement system-driven diseases. Under the terms of the Apellis Agreement, the Company will conduct preclinical research on up to six base editing programs that target specific genes within the complement system in various organs, including the eye, liver, and brain. Apellis has an exclusive option to license any or all of the six programs, or in each case, an Opt-In Right, and will assume responsibility for subsequent development. The Company may elect to enter into a 50-50 U.S. co-development and co-commercialization agreement with Apellis with respect to one program instead of a license. The collaboration is managed on an overall basis by an alliance steering committee formed by an equal number of representatives from the Company and Apellis.

As part of the collaboration, the Company is eligible to receive a total of \$75.0 million in upfront and near-term milestones from Apellis, which is comprised of \$50.0 million received upon signing and an additional \$25.0 million payment on June 30, 2022, the one-year anniversary of the effective date of the Apellis Agreement, or the First Anniversary Payment. Following any exercise of an Opt-In Right for any of the six programs, the Company will be eligible to receive development, regulatory, and sales milestones from Apellis, as well as royalty payments on sales. The collaboration has an initial term of five years and may be extended up to two years on a per year and program-by-program basis. During the collaboration term, Apellis may, subject to certain limitations, substitute a specific complement gene and/or organ for any of the initial base editing programs. Apellis may terminate the Apellis Agreement for convenience on any or all of the programs by providing prior written notice. The Company received the \$50.0 million upfront payment from Apellis in July 2021.

The Company accounts for the Apellis Agreement under ASC 606 as it includes a customer-vendor relationship as defined under ASC 606 and meets the criteria to be considered a contract.

The overall transaction price as of the inception of the contract was determined to be \$75.0 million, which is composed of the upfront payment of \$50.0 million and the First Anniversary Payment of \$25.0 million. The Company will re-evaluate the transaction price in each reporting period. The \$25.0 million for the First Anniversary Payment represents both a contract asset and a contract liability and the Company has presented these amounts net in accordance with ASC 606 guidance for contract assets and liabilities.

The Company concluded that each of the six base editing programs combined with the research and development service, licenses, substitution rights and governance participation were material promises that were both capable of being distinct and were distinct within the context of the Apellis Agreement and represented separate performance obligations. Therefore, the Company did not recognize any upfront revenue related to the license. The Company further concluded that the Opt-In Rights and option to extend the collaboration term did not grant Apellis a material right. The Company determined that the term of the contract is five years, as this is the period during which both parties have enforceable rights.

The selling price of each performance obligation was determined based on the Company's estimated standalone selling price, or the ESSP. The Company developed the ESSP for all of the performance obligations included in the Apellis Agreement with the objective of determining the price at which it would sell such an item if it were to be sold regularly on a standalone basis. The Company allocated the stand-alone selling price to the performance obligations based on the relative standalone selling price method.

The Company recognizes revenue for each performance obligation as it is satisfied over the five-year term using an input method. The Company allocated the transaction price of \$75.0 million to each of the six performance obligations, which includes each of the six base editing programs combined with the research and development service, licenses, substitution rights and governance participation, and is being recognized using an input method based on the actual costs incurred as a percentage of total budgeted costs towards satisfying the performance obligation as this method provides the most faithful depiction of the entity's performance in transferring control of the goods and services promised to Apellis and represents the Company's best estimate of the period of the obligation. For the twelve months ended December 31, 2021, the Company recognized \$1.8 million of revenue related to the Apellis Agreement. As of December 31, 2021, there is \$14.7 million and \$33.5 million of current and long-term deferred revenue, respectively, related to the Apellis Agreement.

#### ***Prime Medicine***

In September 2019, the Company entered into a collaboration and license agreement with Prime Medicine to research and develop a novel gene editing technology developed by one of the Company's founders. Under the terms of the agreement, the Company granted Prime Medicine a non-exclusive license to certain of its CRISPR technology (including Cas12b), delivery technology and certain other technology controlled by the Company to develop and commercialize gene editing products for the treatment of human diseases. Prime Medicine granted the Company an exclusive license to develop and commercialize prime gene editing technology for the creation or modification of any single base transition mutations, as well as any edits made for the treatment of sickle cell disease. The Company is not currently using the intellectual property licensed from Prime Medicine in any of its current programs, but it is required to use commercially reasonable efforts to develop new product candidates using the intellectual property licensed from Prime Medicine. Additionally, each party granted to the other party certain exclusive and non-exclusive licenses to certain technology developed after the effective date of the agreement and controlled by the granting party or jointly owned by the parties. Each party has an obligation to assign rights in certain technology developed under the collaboration to the other party.

For products that use technology licensed from Prime Medicine, the Company is required to make milestone payments to Prime Medicine upon the achievement of certain clinical, regulatory and commercial events. It is also required to use commercially reasonable efforts to develop and seek regulatory approval for two products that use licensed technology from Prime Medicine in certain specified countries and to commercialize any such product(s) for which approval has been obtained in certain specified countries. Prime Medicine and the Company are each required to use commercially reasonable efforts to conduct the activities for which they are responsible under any development plan(s) under the agreement. Prime Medicine has an option to jointly develop and commercialize, and share expenses and revenue for, certain products that use technology licensed from Prime Medicine in the United States. Royalty payments may become due by either party to the other based on the net sales of commercialized products under the agreement. In addition, certain of the rights licensed under the agreement are sublicensed from third parties, and the Company or Prime Medicine may be required to make certain payments to such third parties to the extent the Company or Prime Medicine develop and commercialize products under such rights.

The Company had an obligation to issue \$5.0 million in shares of its common stock to Prime Medicine, and Prime Medicine had an obligation to issue 5,000,000 shares of its common stock to the Company, should the Company elect to extend the collaboration beyond one year. In September 2020, the Company elected to continue the collaboration and, in October 2020, issued 200,307 shares of the Company's common stock to Prime Medicine. The Company recognized \$5.5 million, which represented the fair value of the Company's common stock issued to Prime Medicine, as research and development expense within the accompanying consolidated statements of operations and other comprehensive loss for the year ended December 31, 2020. Additionally, in October 2020, the Company received 5,000,000 shares of Prime Medicine's common stock and recognized \$0.1 million as an offset to research and development expense within the accompanying consolidated statements of operations and other comprehensive loss for the year ended December 31, 2020.

Additionally, the Company provided immaterial interim management and startup services to Prime Medicine through March 2021.

As of December 31, 2021, the Company determined that future milestones and royalties under the agreement were not probable of recognition.

#### **Verve**

In April 2019, the Company entered into a collaboration and license agreement with Verve, or the Verve License Agreement, to investigate gene editing strategies to modify genes associated with an increased risk of coronary diseases. Under the terms of the agreement, the Company granted Verve an exclusive license to certain base editor technology and certain delivery technology and Verve granted the Company a non-exclusive license under certain know-how and patents controlled by Verve, an interest in joint collaboration technology and an exclusive license (except as to Verve) under certain delivery technology. Verve is responsible for all costs associated with the research and development activities under the Verve License agreement. The Company has the option to share in the future development of certain products, with no associated fee at the time the right is exercised. Upon exercise of the Company's option, the profits and expenses of such product will be shared, as defined in the agreement. To date, the Company has not exercised its option.

In connection with the Verve License Agreement, Verve issued the Company 2.6 million shares of its common stock as partial consideration for the licenses granted, having a fair value of \$0.5 million. The fair value of the Verve common stock was determined by management with the assistance of a third-party valuation specialist. In addition, to the extent certain clinical, regulatory, and commercial milestones are met with respect to licensed products, Verve will be required to pay to the Company certain amounts, as defined in the agreement. Either party may owe the other party other milestone payments for certain clinical and regulatory events related to the delivery technology products. Royalty payments may become due by either party to the other based on the net sales of any delivery technology products under the agreement. Lastly, to the extent there are sales of a licensed product, Verve is obligated to pay the Company royalties, as defined in the agreement. The term of the agreement commenced in April 2019 and, unless earlier terminated in accordance with the terms of the agreement, will continue until the last to expire royalty term for any licensed product.

The Company also purchased shares of Verve's Series A preferred stock during the twelve months ended December 31, 2020. During June 2021, Verve completed an initial public offering of its common stock. In connection with Verve's IPO, Verve effected a one-for-9.2592 reverse stock split and also converted all shares of its preferred stock into shares of common stock. As of December 31, 2021 the Company owned 546,970 shares of Verve's common stock valued at \$20.2 million as of December 31, 2021.

Management determined that the performance obligations associated with the Verve License Agreement are the combined licenses and improvements related to the licensed technology. All other items promised to Verve are immaterial in the context of the agreement. The fair value of the shares issued by Verve to the Company were considered a fixed upfront payment of \$0.5 million in the form of non-cash consideration. The Company determined that its performance obligations associated with the Verve License Agreement at contract inception were not distinct and represented a single performance obligation, and that the obligations would be completed over the performance period of the agreement. Accordingly, the upfront payment will be recognized as revenue using a time-based proportional performance model over the contract term (April 2019 through 2038) of the collaboration, as license revenue. For the years ended December 31, 2021, 2020, and 2019, the Company recognized approximately \$24,000, \$24,000 and \$18,000, respectively, of license revenue and has recorded approximately \$0.4 million of deferred revenue at December 31, 2021. To date, no commercial milestone payments or royalties are due. The remaining fees that may be paid under the agreement are considered variable consideration and will be constrained until it is probable that a significant revenue reversal would not occur. To date, the Company has not exercised its option to opt-in to a licensed product and no milestones or royalties have been achieved.

#### **11. Preferred stock and common stock**

In January 2020, the Company authorized the designation of 25,000,000 shares of preferred stock and increased its authorized common stock to 250,000,000 shares, each with a par value of \$0.01 per share.

In February 2020, the Company completed its IPO in which the Company issued and sold 12,176,471 shares of its common stock, including 1,588,235 shares pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of \$17.00 per share, for aggregate gross proceeds of \$207.0 million. The Company received approximately \$188.3 million in net proceeds after deducting underwriting discounts and offering expenses payable by the Company. In connection with the IPO, all outstanding shares of the Company's redeemable convertible preferred stock converted into 29,127,523 shares of the Company's common stock.

In October 2020, the Company issued and sold 5,750,000 shares of its common stock, including 750,000 shares pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of \$23.50 per share, for aggregate gross proceeds of \$135.1 million. The Company received approximately \$126.6 million in net proceeds after deducting underwriting discounts and offering expenses payable by the Company.

In October 2020, due to its election to continue the Prime Agreement, the Company issued 200,307 shares of its common stock to Prime Medicine.

In January 2021, the Company issued and sold 2,795,700 shares of its common stock in a private placement at an offering price of \$93.00 per share for aggregate gross proceeds of \$260.0 million. The Company received \$252.0 million in net proceeds after deducting fees to the placement agents and offering expenses payable by the Company.

In April 2021, the Company entered into the Sales Agreement with Jefferies, pursuant to which the Company was entitled to offer and sell, from time to time at prevailing market prices, shares of the Company's common stock having aggregate gross proceeds of up to \$300.0 million. The Company agreed to pay Jefferies a commission of up to 3.0% of the aggregate gross sale proceeds of any shares sold by Jefferies under the Sales Agreement. As of December 31, 2021, the Company has sold 2,908,009 shares of its common stock under the Sales Agreement at an average price of \$103.16 per share for aggregate gross proceeds of \$300.0 million, before deducting commissions and offering expenses payable by the Company.

In July 2021, the Company and Jefferies entered into an amendment to the Sales Agreement to provide for an increase in the aggregate offering amount under the Sales Agreement, such that as of July 7, 2021, the Company may offer and sell shares of common stock having an aggregate offering price of an additional \$500.0 million. As of December 31, 2021, the Company has sold 1,999,186 additional shares of its common stock under the amended Sales Agreement at an average price of \$105.65 per share for aggregate gross proceeds of \$211.2 million, before deducting commissions and offering expenses payable by the Company, resulting in an aggregate of \$511.2 million in gross proceeds received under the Sales Agreement, as amended, as of December 31, 2021.

In May 2021, the first success payment measurements under each of the Harvard and Broad License Agreements occurred and success payments to Harvard and Broad Institute were calculated to be \$15.0 million and \$15.0 million, respectively. The Company elected to make each payment in shares of the Company's common stock and issued 174,825 shares of the Company's common stock to each of Harvard and Broad Institute to settle these liabilities in June 2021.

The holders of the Company's common stock are entitled to one vote for each share of common stock. Subject to the payment in full of all preferential dividends to which the holders of the Company's preferred stock are entitled, the holders of the Company's common stock shall be entitled to receive ratably dividends out of funds legally available. In the event of any voluntary or involuntary liquidation, dissolution, or winding up of the Company, after the payment or provision for payment of all debts and liabilities of the Company and all preferential amounts to which the holders of Company's preferred stock are entitled with respect to the distribution of assets in liquidation, the holders of common stock shall be entitled to share ratably in the remaining assets of the Company available for distribution.



## 12. Stock option and grant plan

### 2017 stock option and grant plan

In June 2017, the Company's board of directors adopted the Beam Therapeutics Inc. 2017 Stock Option and Grant Plan, or the 2017 Plan, which provided for the grant of qualified incentive stock options and nonqualified stock options, restricted stock or other awards to the Company's employees, officers, directors, advisors, and outside consultants for the issuance or purchase of shares of the Company's common stock. In May 2019, the 2017 Plan was amended to provide up to 8,078,681 shares of common stock for the issuance of stock options and restricted stock.

The 2017 Plan is administered by the board of directors. The exercise prices, vesting and other restrictions are determined at the discretion of the board of directors, except that the exercise price per share of stock options may not be less than 100% of the fair market value of the common stock on the date of grant. Stock options awarded under the 2017 Plan expire 10 years after the grant date, unless the board of directors sets a shorter term. Vesting periods for awards under the 2017 Plan are determined at the discretion of the board of directors. Incentive stock options granted to employees and shares of restricted stock granted to officers, founders and consultants of the Company typically vest over four years. Certain options provide for accelerated vesting if there is a change in control, as defined in the 2017 Plan. Non-statutory options granted to employees, officers, members of the board of directors and consultants of the Company typically vest over four years.

### 2019 incentive plan

In October 2019, the Company's board of directors adopted the Beam Therapeutics Inc. 2019 Equity Incentive Plan, or the 2019 Plan, and, following the IPO, all equity-based awards are granted under the 2019 Plan. The 2019 Plan provides for the grant of qualified and nonqualified stock options, stock appreciation rights, restricted and unrestricted stock and stock units, performance awards, and other share-based awards to the Company's employees, officers, directors, advisors, and outside consultants.

The maximum number of shares of the Company's common stock that may be issued under the 2019 Plan was initially 3,700,000 shares, or the Share Pool, plus the number of shares of the Company's common stock underlying awards under the 2017 Plan, not to exceed 5,639,818 shares, that become available again for grant under the 2017 Plan in accordance with its terms. The Share Pool will automatically increase on January 1st of each year from 2021 to 2029 by the lesser of (i) four percent of the number of shares of the Company's common stock outstanding as of the close of business on the immediately preceding December 31st and (ii) the number of shares determined by the Company's board of directors on or prior to such date for such year.

As of December 31, 2021, the Company had 8,792,459 shares reserved and 1,823,887 shares available for future issuance under the 2019 Plan.

Stock-based compensation expense recorded as research and development and general and administrative expenses in the consolidated statements of operations and other comprehensive loss is as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Research and development	\$ 26,644	\$ 11,199	\$ 4,236
General and administrative	16,926	4,181	2,792
Total stock-based compensation expense	\$ 43,570	\$ 15,380	\$ 7,028

### Stock options

The assumptions used in the Black-Scholes option-pricing model for stock options granted were:

	Years Ended December 31,		
	2021	2020	2019
Expected volatility	71.4-76.7%	75.6-82.6%	86.4-87.6%
Weighted-average risk-free interest rate	1.11 %	1.07 %	2.17 %
Expected dividend yield	0.00 %	0.00 %	0.00 %
Expected term (in years)	6.12	6.24	6.25

A summary of option activity under the Company's equity award plans:

	Number of options	Weighted average exercise price	Weighted average remaining contractual life (years)	Aggregate intrinsic value (1) (in thousands)
Outstanding as of December 31, 2020	5,336,441	\$ 9.70	8.3	\$ 383,901
Granted	1,790,476	88.15		
Exercised	(974,662)	9.88		
Forfeitures	(118,063)	37.65		
Outstanding as of December 31, 2021	<u>6,034,192</u>	32.40	7.9	300,560
Exercisable as of December 31, 2021	<u>2,305,895</u>	11.44	7.2	157,633

(1) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the estimated fair value of the common stock for the options that were in the money as of December 31, 2021 and 2020.

The Company has granted stock options to certain employees to purchase shares of common stock that contain certain performance-based vesting criteria, primarily related to the achievement of certain development milestones related to editing applications, and the closing price of the Company's common stock following an IPO. Recognition of stock-based compensation expense associated with these performance-based stock options commences when the performance condition is considered probable of achievement, using management's best estimates, which consider the inherent risk and uncertainty regarding the future outcomes of the milestones. The expense related to performance-based stock options was immaterial for the years ended December 31, 2021 and 2020 and no expense was recognized for the year ended December 31, 2019.

The weighted-average grant date fair value per share of stock options granted during the years ended December 31, 2021, 2020 and 2019, was \$58.56, \$15.32 and \$6.64, respectively. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2021, 2020 and 2019 was \$85.1 million, \$29.9 million and \$1.6 million, respectively. The weighted-average exercise price of stock options exercised for the years ended December 31, 2021, 2020 and 2019 was \$9.88, \$3.67 and \$1.00, respectively.

As of December 31, 2021, there was \$104.8 million of unrecognized compensation cost related to unvested stock options, which is expected to be recognized over a weighted-average period of approximately 2.3 years.

#### Restricted stock

The Company issued shares of restricted common stock during the year ended December 31, 2021, which consisted only of restricted stock units. The Company issued shares of restricted common stock during the year ended December 31, 2020, which consisted only of restricted stock awards. Restricted common stock issued generally vests over a period of two to four years.

Under the 2017 Plan, the Company granted restricted common stock awards with service conditions. In 2018, the Company issued shares of restricted common stock to certain of the Company's scientific founders and a portion of these issued shares are subject to vesting over a period of four years, with the commencement of vesting of the remaining shares upon the achievement of certain financing milestones, and in certain instances continued service after the milestones are achieved.

If the holders of restricted common stock cease to have a business relationship with the Company, the Company may reacquire any unvested shares of common stock held by these individuals for the original purchase price, and in certain instances for no consideration. The amounts received to date for the purchase price of restricted stock are immaterial. The unvested shares of restricted common stock are not considered outstanding shares for accounting purposes until the shares vest.

The following summarizes the Company's restricted stock activity:

	Shares	Weighted-average grant date fair value
Unvested as of December 31, 2020	1,275,338	\$ 10.95
Issued	885,680	87.50
Vested	(1,020,887)	6.44
Canceled	(13,925)	85.31
Unvested as of December 31, 2021	<u>1,126,206</u>	<u>\$ 74.32</u>

The aggregate fair value of restricted shares that vested during the years ended December 31, 2021, 2020 and 2019 was \$6.4 million, \$6.9 million and \$3.6 million, respectively.

At December 31, 2021, there was approximately \$73.2 million of unrecognized stock-based compensation expense related to restricted stock that is expected to vest. These costs are expected to be recognized over a weighted-average remaining vesting period of 2.9 years.

### 2019 Employee Stock Purchase Plan

In February 2020, the Company's board of directors adopted the Beam Therapeutics Inc. 2019 Employee Stock Purchase Plan, or ESPP, which was approved by the Company's stockholders. Pursuant to the ESPP, certain employees of the Company, excluding consultants and non-employee directors, are eligible to purchase common stock of the Company at a reduced rate during offering periods. The ESPP permits participants to purchase common stock using funds contributed through payroll deductions, subject to a calendar year limit of \$25,000 and at a purchase price of 85% of the lower of the fair market value of the Company's common stock on the first trading day of the offering period or on the applicable purchase date, which will be the final trading day of the applicable purchase period. The first offering period commenced on October 1, 2021 and no shares have been issued yet under the ESPP.

The Company used the Black-Scholes option valuation model to estimate the fair value of the purchase right under the ESPP on the date of grant using the following assumptions:

	For the Offering Period October 1, 2021 - March 31, 2022
Expected volatility	73.07 %
Weighted-average risk-free interest rate	0.05 %
Expected dividend yield	0.00 %
Expected term (in years)	0.50

Expected volatility is based on the historical volatility of the Company's common stock for a period of years corresponding with the expected life of the option. The risk-free interest rate is based on the U.S Treasury yield curve at the time of grant for securities with a maturity period similar to the expected life of the option. The expected life is based on the term of the purchase period for the grants made under the ESPP. The Company uses the straight-line attribution approach to record the expense over the offering period.

Stock-based compensation expense for the ESPP for the year ended December 31, 2021 was \$0.3 million.

As of December 31, 2021, the Company had 1,049,460 shares available for issuance under the ESPP.

### 13. Net loss per share attributable to common stockholders

As noted above, for periods in which the Company reports a net loss attributable to common stockholders, potentially dilutive securities have been excluded from the computation of diluted net loss per share as their effects would be anti-dilutive. Therefore, the weighted average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The Company excluded the following potential common shares, presented based on amounts outstanding at period end, from the computation of diluted net loss per share attributable to common stockholders because including them would have had an anti-dilutive effect:

	2021	December 31, 2020	2019
Redeemable convertible preferred stock	—	—	29,127,523
Unvested restricted stock	1,126,206	1,275,338	2,655,806
Outstanding options to purchase common stock	6,034,192	5,336,441	4,791,047
ESPP	19,379	—	—
Total	<u>7,179,777</u>	<u>6,611,779</u>	<u>36,574,376</u>

The following table summarizes the computation of basic and diluted net loss per share attributable to common stockholders of the Company (in thousands, except share and per share amounts):

	2021	Years Ended December 31, 2020	2019
<b>Numerator:</b>			
Net loss	\$ (370,638)	\$ (194,592)	\$ (78,326)
Accretion of redeemable convertible preferred stock to redemption value, including dividends on preferred stock	—	(1,277)	(12,714)
Net loss attributable to common stockholders	<u>(370,638)</u>	<u>(195,869)</u>	<u>(91,040)</u>
<b>Denominator:</b>			
Weighted average number of common shares, basic and diluted	64,227,676	46,733,221	6,479,591
Net loss per common share attributable to common stockholders, basic and diluted	<u>\$ (5.77)</u>	<u>\$ (4.19)</u>	<u>\$ (14.05)</u>

## 14. Income taxes

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

	Years Ended December 31,		
	2021	2020	2019
Federal statutory rate	21.0%	21.0%	21.0%
State income taxes, net of federal benefit	5.1	7.2	7.4
Research and development tax credits	2.6	2.1	3.1
Nondeductible/ nontaxable permanent items	0.7	0.8	(1.8)
IPR&D Guide Acquisition	(8.8)	—	—
Change in valuation allowance	(20.6)	(31.1)	(29.7)
Total	0.0%	0.0%	0.0%

The components of the Company's deferred taxes are as follows (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	\$ 103,868	\$ 58,338
Research and development tax credits	23,745	8,756
Accrued expenses and other	2,810	1,445
Derivative liabilities	11,483	19,421
Stock options	5,489	1,975
Amortization	20,754	2,079
Lease liability	38,734	27,340
Total deferred tax assets	206,883	119,354
ROU asset	(27,950)	(23,692)
Property and equipment	(1,868)	(558)
Other	(4,954)	(141)
Less: valuation allowance	(172,111)	(94,963)
Deferred tax assets, net	\$ —	\$ —

The Company had no income tax expense due to the operating losses incurred for the years ended December 31, 2021, 2020, and 2019. Management has evaluated the positive and negative evidence bearing upon the realizability of the Company's net deferred tax assets and has determined that it is more likely than not that the Company will not recognize the benefits of the net deferred tax assets. As a result, the Company has recorded a full valuation allowance at December 31, 2021 and 2020. The valuation allowance increased by \$77.1 million in 2021, due to the increase in deferred tax assets, primarily due to net operating loss carryforwards, and research and development tax credits, amortization expenses and the fair value of the derivative liability. The valuation allowance increased by \$58.5 million in 2020.

As of December 31, 2021, the Company had \$386.0 million of federal and \$360.9 million of state net operating loss carryforwards. If not utilized, both the federal and state net operating loss carryforwards expire starting in 2037. Included in the \$386.0 million federal net operating loss carryforwards is \$382.6 million of net operating loss generated in 2018 through 2021 that will not expire. Additionally, as of December 31, 2021, the Company had \$17.1 million of federal and \$8.4 million of Massachusetts tax credits that expire starting in 2038 and 2033, respectively.

As of December 31, 2021, and 2020, the Company had no uncertain tax positions. The Company recognizes both interest and penalties associated with unrecognized tax benefits as a component of income tax expense. The Company has not recorded any interest or penalties for unrecognized tax benefits since its inception.

The Company filed income tax returns in the United States and the Commonwealth of Massachusetts in all tax years since inception. Tax years beginning in 2017 remain open to examination in these jurisdictions, as carryforward attributes generated in past years may be adjusted in a future period. The IRS has not made any assessments as of December 31, 2021.

## 15. Related party transactions

### Founders

For the years ended December 31, 2021, 2020 and 2019, the Company made payments of \$0.5 million, \$0.5 million and \$0.5 million, respectively, to its three founder shareholders for scientific consulting and other expenses.

### Verve

The Company and Verve are parties to a collaboration and license agreement and have a common board member.

Prior to Verve's initial public offering in June 2021, the Company owned both common and preferred shares of Verve and valued such investment based on the cost of the equity securities adjusted for any observable market transactions. Following the initial public offering, and the conversion to common stock and the stock split, the equity securities have a readily determinable fair value and the Company owned 546,970 shares of Verve's common stock, the value of which is included in marketable securities in the consolidated balance sheet. The Company recorded the investment at fair value as of December 31, 2021, which resulted in the recognition of \$17.7 million of other income for the twelve months ended December 31, 2021. The value of this investment as of December 31, 2021 is \$20.2 million. During the year ended December 31, 2020, the Company recognized unrealized gains of \$0.5 million on its investment in Verve preferred stock.

During the years ended December 31, 2020 and 2019, the Company purchased shares of Verve series A preferred stock valued at \$0.8 million and \$0.4 million, respectively. These shares were converted into shares of Verve common stock in connection with Verve's initial public offering.

The Company purchased certain materials from Verve amounting to \$0.2 million and \$0.4 million, which is recorded as research and development expenses within the accompanying consolidated statements of operations and other comprehensive loss for the years ended December 31, 2021 and 2020, respectively. The Company also sold certain materials to Verve amounting to \$0.2 million, which is recorded as interest and other income (expense), net within the accompanying consolidated statements of operations and other comprehensive loss for the year ended December 31, 2020.

In October 2021, the Company entered into an agreement pursuant to which Verve subleased 12,000 square feet of the Company's existing office and laboratory space for a term of one year which began in December 2021. Verve is expected to pay approximately \$1.4 million in rental payments over the term of the sublease, as well as its proportionate costs for the landlord's operating expense, insurance, property taxes, and utilities. The Company recorded \$0.1 million of sublease income related to this sublease within the accompanying consolidated statements of operations and other comprehensive loss for the year ended December 31, 2021.

### ***Prime Medicine***

The Company and Prime Medicine are parties to a collaboration and license agreement and have a common founder and common board member.

In September 2020, the Company elected to continue its collaboration with Prime Medicine and, in October 2020, as required by the terms under its collaboration and license agreement with Prime Medicine, issued 200,307 shares of the Company's common stock to Prime Medicine. The Company recognized \$5.5 million, which represents the fair value of the Company's common stock issued to Prime Medicine, as research and development expense within the accompanying consolidated statements of operations and other comprehensive loss for the year ended December 31, 2020. Additionally, in October 2020, the Company received 5,000,000 shares of Prime Medicine's common stock and recognized \$0.1 million as an offset to research and development expense within the accompanying consolidated statements of operations and other comprehensive loss for the year ended December 31, 2020.

Management services provided to the Company by Prime Medicine were immaterial for the year ended December 31, 2021. Additionally, in September 2019, in connection with the Company's collaboration and license agreement with Prime Medicine, the Company executed a letter agreement, as amended, to provide certain interim management and startup services to Prime Medicine through March 2021. Prime Medicine is obligated to reimburse the Company's out-of-pocket costs incurred in connection with performing the services and, beginning in October 2020 and ending March 2021, paid the Company a \$30,000 monthly service fee. For the years ended December 31, 2021 and 2020, the Company recognized \$0.1 million and \$0.1 million, respectively, for performing such services in interest and other income (expense), net, within the accompanying consolidated statements of operations and other comprehensive loss.

### **16. Employee benefits**

In 2018, the Company established a defined-contribution plan under Section 401(k) of the Internal Revenue Code, or 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. Beginning January 1, 2020, the Company made matching contributions equal to 50% of the employee's contributions, subject to a maximum of 6% of eligible compensation. The Company made matching contributions of \$1.1 million for the year ended December 31, 2021.

**BEAM THERAPEUTICS INC.**  
**AMENDED AND RESTATED 2019 EMPLOYEE STOCK PURCHASE PLAN**

### **1. Defined Terms**

Exhibit A, which is incorporated by reference, defines the terms used in the Plan and sets forth certain operational rules related to those terms.

### **2. Purpose of Plan**

The Plan is intended to enable Eligible Employees to use payroll deductions to purchase shares of Stock in offerings under the Plan, and thereby acquire an interest in the Company. The Plan is intended to qualify as an “employee stock purchase plan” under Section 423 and to be exempt from the application and requirements of Section 409A of the Code, and is to be construed accordingly.

### **3. Options to Purchase Stock**

Subject to adjustment pursuant to Section 16 of the Plan, the maximum aggregate number of shares of Stock available for purchase pursuant to the exercise of Options granted under the Plan will be 465,000 shares (the “**Initial Share Pool**”). The Initial Share Pool will automatically increase on January 1<sup>st</sup> of each year from 2020 to 2029 by the lesser of (i) one percent of the number of shares of Stock outstanding as of the close of business on the immediately preceding December 31<sup>st</sup> and (ii) the number of shares of Stock determined by the Board on or prior to such date for such year up to a maximum of 5,083,204 shares in the aggregate (the Initial Share Pool, as it may be so increased, the “**Share Pool**”). The shares of Stock to be delivered upon exercise of Options under the Plan may be either shares of authorized but unissued Stock, treasury Stock, or previously issued Stock acquired by the Company. If any Option granted under the Plan expires or terminates for any reason without having been exercised in full or ceases for any reason to be exercisable in whole or in part, the unpurchased shares of Stock subject to such Option will not reduce the Share Pool and will again be available for purchase under the Plan. If, on an Exercise Date, the total number of shares of Stock that would otherwise be subject to Options granted under the Plan exceeds the number of shares then available in the Share Pool, the Administrator shall make a pro rata allocation of the shares remaining available for purchase under the Plan in as uniform a manner as is practicable and as it determines to be equitable. In such event, the Administrator shall notify each Participant of such reduction and of the effect on the Participant’s Options and may reduce the rate of a Participant’s payroll deductions, if necessary.

### **4. Eligibility**

(a) *Eligibility Requirements.* Subject to Section 13 of the Plan, and the exceptions and limitations set forth in Section 4(b), Section 4(c), and Section 6 of the Plan, or as may be provided elsewhere in the Plan, each Employee (i) who has been continuously employed by the Company or a Designated Subsidiary, as applicable, for a period of at least ninety (90) calendar days as of the first day of an Option Period, (ii) whose customary Employment with the Company or a Designated Subsidiary, as applicable, is for more than five (5) months per calendar year, (iii) who customarily works twenty (20) hours or more per week, and (iv) who satisfies the requirements set forth in the Plan will be an Eligible Employee.

(b) *Five Percent Shareholders.* No Employee may be granted an Option under the Plan if, immediately after the Option is granted, the Employee would own (or pursuant to Section 424(d) of the Code would be deemed to own) stock possessing five percent (5%) or more of the total combined voting power or value of all classes of stock of the Company or of its Parent or Subsidiaries, if any.

(c) *Additional Requirements.* The Administrator may, for Option Periods that have not yet commenced, establish additional or other eligibility requirements, or amend the eligibility requirements set forth in subsection (a) above, in each case, consistent with the requirements of Section 423.

## 5. Option Periods

The Plan will generally be implemented by a series of separate offerings referred to as “**Option Periods**”. Unless otherwise determined by the Administrator, the Option Periods will be successive periods of approximately six (6) months commencing on the first Business Day in January and July of each year, anticipated to be on or around January 1 and July 1, and ending approximately six months later on the last Business Day in June or December, as applicable, of each year, anticipated to be on or around June 30 and January 31. The last Business Day of each Option Period will be an “**Exercise Date**”. The Administrator may change the Exercise Date, the commencement date, the ending date and the duration of each Option Period, in each case, to the extent permitted by Section 423; *provided, however*, that no Option may be exercised after 27 months from its grant date.

## 6. Option Grant

Subject to the limitations set forth in Sections 4 and 10 of the Plan and the Maximum Share Limit, on the first day of an Option Period, each Participant automatically will be granted an Option to purchase shares of Stock on the Exercise Date; *provided, however*, that no Participant will be granted an Option under the Plan that permits the Participant’s right to purchase shares of Stock under the Plan and under all other employee stock purchase plans of the Company and its Parent and Subsidiaries, if any, to accrue at a rate that exceeds \$25,000 in Fair Market Value (or such other maximum as may be prescribed from time to time by the Code) for each calendar year during which any Option granted to such Participant is outstanding at any time, as determined in accordance with Section 423(b)(8) of the Code.

## 7. Method of Participation

(a) *Payroll Deduction and Participation Authorization.* To participate in an Option Period, an Eligible Employee must execute and deliver to the Administrator a payroll deduction and participation authorization form in accordance with the procedures prescribed by, and in a form acceptable to, the Administrator and, in so doing, the Eligible Employee will thereby become a Participant as of the first day of such Option Period. Such an Eligible Employee will remain a Participant with respect to subsequent Option Periods until his or her participation in the Plan is terminated as provided herein. Such payroll deduction and participation authorization must be delivered not later than fourteen (14) calendar days prior to the first day of an Option Period, or such other time as specified by the Administrator.

(b) *Changes to Payroll Deduction Authorization for Subsequent Option Periods.* A Participant's payroll deduction authorization will remain in effect for subsequent Option Periods unless the Participant files a new authorization not later than fourteen (14) calendar days prior to the first day of the subsequent Option Period (or such other time as specified by the Administrator) or the Participant's Option is cancelled pursuant to Section 13 or Section 14 of the Plan.

(c) *Changes to Payroll Deduction Authorization for Current Option Period.* During an Option Period, a Participant's payroll deduction authorization (i) may not be increased, but (ii) may be decreased on the terms and subject to the conditions established by the Administrator. A Participant may terminate his or her payroll deduction authorization at any time during an Option Period by canceling his or her Option in accordance with Section 13 of the Plan.

(d) *Payroll Deduction Percentage.* Each payroll deduction authorization will authorize payroll deductions as a whole percentage from 1% up to 20% of the employee's Eligible Compensation per payroll period, with the high end of the permitted payroll deduction percentage subject to reduction by the Administrator on or prior to the beginning of an Option Period.

(e) *Payroll Deduction Account.* All payroll deductions made pursuant to this Section 7 will be credited to the Participant's Account. Amounts credited to a Participant's Account will not be required to be set aside in trust or otherwise segregated from the Company's general assets.

## **8.Method of Payment**

A Participant must pay for shares of Stock purchased under the Plan with accumulated payroll deductions credited to the Participant's Account.

## **9.Purchase Price**

The Purchase Price of shares of Stock issued pursuant to the exercise of an Option on each Exercise Date will be eighty-five percent (85%) (or such greater percentage specified by the Administrator to the extent permitted under Section 423) of the lesser of (a) the Fair Market Value of a share of Stock on the date on which the Option was granted pursuant to Section 6 of the Plan (*i.e.*, the first day of the Option Period) and (b) the Fair Market Value of a share of Stock on the date on which the Option is deemed exercised pursuant to Section 10 of the Plan (*i.e.*, the Exercise Date).



## 10. Exercise of Options

(a) *Purchase of Shares.* Subject to the limitations set forth in Section 6 of the Plan and this Section 10, with respect to each Option Period, on the applicable Exercise Date, each Participant will be deemed to have exercised his or her Option and the accumulated payroll deductions in the Participant's Account will be applied to purchase the greatest number of shares of Stock (rounded down to the nearest whole share) that can be purchased with such Account balance at the applicable Purchase Price; *provided, however*, that no more than 5,000 shares of Stock may be purchased by a Participant on any Exercise Date, or such lesser number as the Administrator may prescribe in accordance with Section 423 (the "**Maximum Share Limit**"). As soon as practicable thereafter, shares of Stock so purchased will be placed, in book-entry form, into a record keeping account in the name of the Participant. No fractional shares will be purchased pursuant to the exercise of an Option under the Plan; any accumulated payroll deductions in a Participant's Account that are not sufficient to purchase a whole share will be retained in the Participant's Account for the subsequent Option Period, subject to earlier withdrawal by the Participant as provided in Section 13 hereof.

(b) *Return of Account Balance.* Except as provided in Section 10(a) above with respect to fractional shares, any accumulated amount of payroll deductions in a Participant's Account for an Option Period that are not used for the purchase of shares of Stock, whether because of the Participant's withdrawal from participation in an Option Period or for any other reason, will be returned to the Participant (or his or her designated beneficiary or legal representative, as applicable), without interest, as soon as administratively practicable after such withdrawal or other event, as applicable. If the Participant's accumulated payroll deductions on the Exercise Date of an Option Period would otherwise enable the Participant to purchase shares of Stock in excess of the Maximum Share Limit or the maximum Fair Market Value set forth in Section 6 of the Plan, the excess of the amount of the accumulated payroll deductions over the aggregate Purchase Price of the shares of Stock actually purchased will be returned to the Participant, without interest, as soon as administratively practicable after such Exercise Date.

## 11. Interest

No interest will accrue or be payable on any amount held in the Account of any Participant.

## 12. Taxes

Payroll deductions will be made on an after-tax basis. The Administrator will have the right to make such provision as it deems necessary for, and may condition the exercise of an Option on, the satisfaction of its obligations to withhold federal, state, local income or other taxes incurred by reason of the purchase or disposition of shares of Stock under the Plan. In the Administrator's discretion and subject to applicable law, such tax obligations may be satisfied in whole or in part by delivery of shares of Stock to the Company, including shares of Stock purchased under the Plan, valued at Fair Market Value, but not in excess of the maximum withholding amount consistent with the award being subject to equity accounting treatment under the Accounting Rules.

### **13. Cancellation and Withdrawal**

(a) *Cancellation of Payroll Deduction Authorization and Withdrawal from Plan.* A Participant who has been granted an Option under the Plan may cancel all (but not less than all) of such Option and terminate his or her participation in the Plan by notice to the Administrator in accordance with the procedures prescribed by, and in a form acceptable to, the Administrator. To be effective with respect to an upcoming Exercise Date, such cancellation notice must be delivered not later than fourteen (14) calendar days prior to such Exercise Date (or such other time as specified by the Administrator). Upon such termination and cancellation, the balance in the Participant's Account will be returned to the Participant, without interest, as soon as administratively practicable thereafter. For the avoidance of doubt, a Participant who reduces his or her withholding rate for a future Option Period to 0% pursuant to Section 7 of the Plan will be deemed to have terminated his or her payroll deduction authorization and canceled his or her participation in the Plan as to such Option Period and all future Option Periods, unless the Participant delivers a new payroll deduction authorization for a subsequent Option Period in accordance with the rules of Section 7(b) of the Plan.

(b) *401(k) Hardship Withdrawal.* To the extent a suspension of contribution is required by a 401(k) Plan maintained by the Company or a Subsidiary, a Participant who makes a hardship withdrawal from such 401(k) Plan shall be deemed to have terminated his or her payroll deduction authorization as of the date of such hardship withdrawal, shall cease to be a Participant as of such date, shall be deemed to have canceled any outstanding Options, and shall not be permitted to participate in the Plan until the first Option Period commencing after the suspension of contributions ceases to apply to the Participant.

### **14. Termination of Employment; Death of Participant**

Upon the termination of a Participant's employment with the Company or a Designated Subsidiary, as applicable, for any reason (including the death of a Participant during an Option Period prior to an Exercise Date) or in the event the Participant ceases to qualify as an Eligible Employee, the Participant will cease to be a Participant, any Option held by the Participant under the Plan will be canceled, the balance in the Participant's Account will be returned to the Participant (or his or her estate or designated beneficiary in the event of the Participant's death), without interest, as soon as administratively practicable thereafter, and the Participant will have no further rights under the Plan.

### **15. Equal Rights; Participant's Rights Not Transferable**

All Participants granted Options in an offering under the Plan will have the same rights and privileges, consistent with the requirements set forth in Section 423. Any Option granted under the Plan will be exercisable during the Participant's lifetime only by him or her and may not be sold, pledged, assigned, or transferred in any manner. In the event any Participant violates or attempts to violate the terms of this Section 15, as determined by the Administrator in its sole discretion, any Options granted to the Participant under the Plan may be terminated by the Company and, upon the return to the Participant of the balance of his or her Account, without interest, all of the Participant's rights under the Plan will terminate.

## 16. Change in Capitalization; Corporate Transaction

(a) *Change in Capitalization.* In the event of a stock dividend, stock split or combination of shares (including a reverse stock split), recapitalization or other change in the Company's capital structure that constitutes an equity restructuring within the meaning of the Accounting Rules, the Administrator shall make appropriate adjustments to the aggregate number and type of shares of stock available under the Plan, the number and type of shares of stock granted under any outstanding Options, the maximum number and type of shares of stock purchasable under any outstanding Option, and/or the Purchase Price under any outstanding Option, in any case, in a manner that complies with Section 423.

(b) *Corporate Transaction.* In the event of a sale of all or substantially all of the Stock or a sale of all or substantially all of the assets of the Company, or a merger or similar transaction in which the Company is not the surviving corporation or that results in the acquisition of the Company by another person, the Administrator may, in its discretion, (i) if the Company is merged with or acquired by another corporation, provide that each outstanding Option will be assumed or exchanged for a substitute Option granted by the acquiror or successor corporation or by a parent or subsidiary of the acquiror or successor corporation, (ii) cancel each outstanding Option and return the balances in Participants' Accounts to the Participants, and/or (iii) pursuant to Section 18 of the Plan, terminate the Option Period on or before the date of the proposed sale, merger or similar transaction.

## 17. Administration

The Plan will be administered by the Administrator. The Administrator has discretionary authority, subject only to the express provisions of the Plan, to administer and interpret the Plan; to determine eligibility under the Plan; to prescribe forms, rules and procedures relating to the Plan; and to otherwise do all things necessary or desirable to carry out the purposes of the Plan. Determinations of the Administrator made with respect to the Plan are conclusive and bind all persons.

The Administrator may specify the manner in which the Company and/or Employees are to provide notices and forms under the Plan, and may require that such notices and forms be submitted electronically.

## 18. Amendment and Termination of Plan

(a) *Amendment.* The Administrator reserves the right at any time or times to amend the Plan to any extent and in any manner it may deem advisable; *provided, however*, that any amendment that would be treated as the adoption of a new plan for purposes of Section 423 will have no force or effect unless approved by the shareholders of the Company within 12 months before or after its adoption.

(b) *Termination.* The Administrator reserves the right at any time or times to suspend or terminate the Plan. In connection therewith, the Administrator may provide, in its sole discretion, either that outstanding Options will be exercisable either on the Exercise Date for the applicable Option Period or on such earlier date as the Board may specify (in which case such earlier date will be treated as the Exercise Date for the applicable Option Period), or that the balance of each Participant's Account will be returned to the Participant, without interest.

## **19.Approvals**

Shareholder approval of the Plan will be obtained prior to the date that is twelve (12) months after the date of Board approval. In the event that the Plan has not been approved by the shareholders of the Company prior to September 25, 2020, all Options to purchase shares of Stock under the Plan will be cancelled and become null and void.

Notwithstanding anything herein to the contrary, the obligation of the Company to issue and deliver shares of Stock under the Plan will be subject to the approval required of any governmental authority in connection with the authorization, issuance, sale or transfer of such shares of Stock and to any requirements of any national securities exchange applicable thereto, and to compliance by the Company with other applicable legal requirements in effect from time to time.

## **20.Participants' Rights as Shareholders and Employees**

A Participant will have no rights or privileges as a shareholder of the Company and will not receive any dividends in respect of any shares of Stock covered by an Option granted hereunder until such Option has been exercised, full payment has been made for such shares, and the shares have been issued to the Participant.

Nothing contained in the provisions of the Plan will be construed as giving to any Employee the right to be retained in the employ of the Company or any Designated Subsidiary or as interfering with the right of the Company or any Designated Subsidiary to discharge, promote, demote or otherwise re-assign any Employee from one position to another within the Company or any Designated Subsidiary at any time.

## **21.Restrictions on Transfer; Information Regarding Disqualifying Dispositions.**

(a) *Restrictions on Transfer.* Shares of Stock purchased under the Plan may, in the discretion of the Administrator, be subject to a restriction prohibiting the transfer, sale, pledge or alienation of such shares of Stock by a Participant, other than by will or by the laws of descent and distribution, for such period following such purchase as may be determined by the Administrator.

(b) *Disqualifying Dispositions.* By electing to participate in the Plan, each Participant agrees to provide such information about any transfer of Stock acquired under the Plan that occurs within two years after the first day of the Option Period in which such Stock was acquired and within one year after the day such Stock was purchased as may be requested by the Company or any Designated Subsidiary in order to assist it in complying with applicable tax laws.

## 22. Miscellaneous

(a) *Waiver of Jury Trial.* By electing to participate in the Plan, each Participant waives (or will be deemed to have waived), to the maximum extent permitted under applicable law, any right to a trial by jury in any action, proceeding or counterclaim concerning any rights under the Plan or with respect to any Option, or under any amendment, waiver, consent, instrument, document or other agreement delivered or which in the future may be delivered in connection therewith, and agrees (or will be deemed to have agreed) that any such action, proceedings or counterclaim will be tried before a court and not before a jury. By electing to participate in the Plan, each Participant certifies that no officer, representative, or attorney of the Company has represented, expressly or otherwise, that the Company would not, in the event of any action, proceeding or counterclaim, seek to enforce the foregoing waivers. Notwithstanding anything to the contrary in the Plan, nothing herein is to be construed as limiting the ability of the Company and a Participant to agree to submit any dispute arising under the terms of the Plan or in respect of any Option to binding arbitration or as limiting the ability of the Company to require any individual to agree to submit such disputes to binding arbitration as a condition of receiving an Option hereunder.

(b) *Limitation of Liability.* Notwithstanding anything to the contrary in the Plan, neither the Company, nor any of its subsidiaries, nor the Administrator, nor any person acting on behalf of the Company, any of its subsidiaries, or the Administrator, will be liable to any Participant, to any permitted transferee, to the estate or beneficiary of any Participant or any permitted transferee, or to any other person by reason of any acceleration of income, any additional tax, or any penalty, interest or other liability asserted by reason of the failure of the Plan or any Option to satisfy the Requirements of Section 423, or otherwise asserted with respect to the Plan or any Option.

(c) *Unfunded Plan.* The Company's obligations under the Plan are unfunded, and no Participant will have any right to specific assets of the Company in respect of any Option. Participants will be general unsecured creditors of the Company with respect to any amounts due or payable under the Plan.

## 23. Establishment of Sub-Plans

Notwithstanding the foregoing or any provision of the Plan to the contrary, consistent with the requirements of Section 423, the Administrator may, in its sole discretion, amend the terms of the Plan, or an offering and/or provide for separate offerings under the Plan in order to, among other things, reflect the impact of local law outside of the United States as applied to one or more Eligible Employees of a Designated Subsidiary and may, where appropriate, establish one or more sub-plans to reflect such amended provisions.

## 24. Governing Law

(a) *Certain Requirements of Corporate Law.* Options and shares of Stock will be granted, issued and administered consistent with the requirements of applicable Delaware law relating to the issuance of stock and the consideration to be received therefor, and with the applicable requirements of the stock exchanges or other trading systems on which the Stock is listed or entered for trading, in each case as determined by the Administrator.

(b) *Other Matters.* Except as otherwise provided by the express terms of a sub-plan described in Section 23 or as provided in Section 24(a), the domestic substantive laws of the Commonwealth of Massachusetts govern the provisions of the Plan and of Options under the Plan and all claims or disputes arising out of or based upon the Plan or any Option or relating to the subject matter hereof or thereof without giving effect to any choice or conflict of laws provision or rule that would cause the application of the domestic substantive laws of any other jurisdiction.

(c) *Jurisdiction.* By electing to participate in the Plan, each Participant agrees or will be deemed to have agreed to (i) submit irrevocably and unconditionally to the jurisdiction of the federal and state courts located within the geographic boundaries of the United States District Court for the District of Massachusetts for the purpose of any suit, action or other proceeding arising out of or based upon the Plan or any Option; (ii) not commence any suit, action or other proceeding arising out of or based upon the Plan or any Option, except in the federal and state courts located within the geographic boundaries of the United States District Court for the District of Massachusetts; and (iii) waive, and not assert, by way of motion as a defense or otherwise, in any such suit, action or proceeding, any claim that he or she is not subject personally to the jurisdiction of the above-named courts that his or her property is exempt or immune from attachment or execution, that the suit, action or proceeding is brought in an inconvenient forum, that the venue of the suit, action or proceeding is improper or that the Plan or any Option or the subject matter thereof may not be enforced in or by such court.

## 25. Effective Date and Term

The Plan will become effective upon adoption of the Plan by the Board and no rights will be granted hereunder after the earliest to occur of (a) the Plan's termination by the Company, (b) the issuance of all shares of Stock available for issuance under the Plan or (c) the day before the 10-year anniversary of the date the Board approves the Plan.

**EXHIBIT A**  
**Definition of Terms**

The following terms, when used in the Plan, will have the meanings and be subject to the provisions set forth below:

**“401(k) Plan”:** A savings plan qualifying under Section 401(k) of the Code that is sponsored by the Company or one of its Subsidiaries for the benefit of its employees.

**“Account”:** A notional payroll deduction account maintained in the Participant’s name on the books of the Company.

**“Accounting Rules”:** Financial Accounting Standards Board Accounting Standards Codification Topic 718, or any successor provision.

**“Administrator”:** The Compensation Committee of the Board, except that the Compensation Committee may delegate its authority under the Plan to a sub-committee comprised of one or more of its members, to members of the Board, or to officers or employees of the Company to the extent permitted by applicable law. In each case, references herein to the Administrator refer, as applicable, to such persons or groups so delegated to the extent of such delegation.

**“Board”:** The Board of Directors of the Company.

**“Business Day”:** Any day on which the established national exchange or trading system (including the Nasdaq Global Market) on which the Stock is traded is available and open for trading.

**“Code”:** The U.S. Internal Revenue Code of 1986, as from time to time amended and in effect, or any successor statute as from time to time in effect.

**“Company”:** Beam Therapeutics Inc, a Delaware corporation.

**“Designated Subsidiary”:** A Subsidiary of the Company that has been designated by the Board or the Compensation Committee of the Board from time to time as eligible to participate in the Plan, as set forth on Exhibit B. For the avoidance of doubt, any Subsidiary of the Company shall be eligible to be designated as a Designated Subsidiary hereunder.

**“Effective Date”:** The date set forth in Section 23 of the Plan.

**“Eligible Compensation”:** Regular base salary or regular base wages (excluding, for the avoidance of doubt, overtime payments, bonuses, stipends, reimbursements, long-term disability or family and medical leave payments, commissions and sales incentives and any long-term or equity-based incentive payments or awards). Eligible Compensation will not be reduced by any income or employment tax withholdings or any contributions by the Employee to a 401(k) Plan or a plan under Section 125 of the Code, but will be reduced by any contributions made on the Employee’s behalf by the Company or any Subsidiary to any deferred compensation plan or welfare benefit program now or hereafter established.

**“Eligible Employee”:** Any Employee who meets the eligibility requirements set forth in Section 4 of the Plan.

**“Employee”:** Any person who is employed by the Company or a Designated Subsidiary. For the avoidance of doubt, independent contractors and consultants are not “Employees”.

**“Exercise Date”:** The date set forth in Section 5 of the Plan or otherwise designated by the Administrator with respect to a particular Option Period on which a Participant will be deemed to have exercised the Option granted to him or her for such Option Period.

**“Fair Market Value”:**

(a) If the Stock is readily traded on an established national exchange or trading system (including the NASDAQ Global Market), the closing price of a share of Stock as reported by the principal exchange on which such Stock is traded; *provided, however,* that if such day is not a trading day, Fair Market Value will mean the reported closing price of a share of Stock for the immediately preceding day that is a trading day.

(b) If the Stock is not traded on an established national exchange or trading system, the average of the bid and ask prices for shares Stock where the bid and ask prices are quoted.

(c) If the Stock cannot be valued pursuant to clauses (a) or (b), the value as determined in good faith by the Board in its sole discretion.

**“Maximum Share Limit”:** The meaning set forth in Section 10 of the Plan.

**“Option”:** An option granted pursuant to the Plan entitling the holder to acquire shares of Stock upon payment of the Purchase Price per share of Stock.

**“Option Period”:** An offering period established in accordance with Section 5 of the Plan.

**“Parent”:** A “parent corporation” as defined in Section 424(e) of the Code.

**“Participant”:** An Eligible Employee who elects to participate in an Option Period under the Plan.



**“Plan”:** The Beam Therapeutics Inc. Amended and Restated 2019 Employee Stock Purchase Plan, as from time to time amended and in effect.

**“Purchase Price”:** The price per share of Stock with respect to an Option Period determined in accordance with Section 9 of the Plan.

**“Section 423”:** Section 423 of the Code and the regulations thereunder.

**“Stock”:** Common stock of the Company, par value \$0.01 per share.

**“Subsidiary”:** A “subsidiary corporation” as defined in Section 424(f) of the Code.

**EXHIBIT B**  
**Designated Subsidiaries**

Designated Subsidiaries as of the date of adoption of the Plan by the Board are listed below:

N/A

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FIRST AMENDMENT TO LEASE

This First Amendment to Lease (this "**First Amendment**") is made as of April 14<sup>th</sup>, 2020 by and between MASSACHUSETTS INSTITUTE OF TECHNOLOGY, a Massachusetts charitable corporation with an address of c/o MIT Investment Management Company, One Broadway, Suite 09-200, Cambridge, MA 02142 ("**Landlord**") and BEAM THERAPEUTICS, INC., a Delaware corporation with an address of 26 Lansdowne Street, 2<sup>nd</sup> Floor, Cambridge, MA 02139 ("**Tenant**").

## WITNESSETH

WHEREAS, Landlord and Tenant are the current parties to that certain Lease dated April 24, 2019 (the "**Lease**") pursuant to which Landlord is leasing to Tenant approximately 123,209 rentable square feet (as more particularly described in the Lease, the ("**Original Space**") located on the seventh, eighth, ninth and tenth floors of the Laboratory Addition to the building located at 238 Main Street, Cambridge, MA;

WHEREAS, Tenant has notified Landlord that it does not wish to have a vivarium constructed as part of Tenant's Fitout and accordingly, the Final Construction Drawings with respect to Phase 2 will vary from the approved Design Development Plans for such Phase because the vivarium will be removed therefrom; and

WHEREAS, Landlord and Tenant wish to memorialize their agreements with respect thereto.

NOW, THEREFORE, in consideration of the covenants herein reserved and contained, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **Recitals; Capitalized Terms.** The foregoing recitals are hereby incorporated by reference. All capitalized terms not otherwise defined herein shall have the meanings ascribed to them as set forth in the Lease.

2. **Premises.** Notwithstanding anything to the contrary contained in the Lease, but subject to Section 25.16 of the Lease, from and after the date hereof, the "**Premises**" shall mean approximately 122,620 rentable square feet of space consisting of all rentable areas on the seventh (7<sup>th</sup>) floor of the Laboratory Addition (containing approximately 30,655 rentable square feet), all rentable areas on the eighth (8<sup>th</sup>) floor of the Laboratory Addition (containing approximately 30,655 rentable square feet), all rentable areas on the ninth (9<sup>th</sup>) floor of the Laboratory Addition (containing approximately 30,655 rentable square feet), all rentable areas on the tenth (10<sup>th</sup>) floor of the Laboratory Addition (containing approximately 30,655 rentable square feet), including associated mechanical, ground floor and lower level space, all as more particularly shown as hatched, highlighted or outlined on the Lease Plan.

3. **Base Rent.** Notwithstanding anything to the contrary contained in the Lease, from and after the date hereof, the Base Rent schedule with respect to Phase 2 in the Lease Summary Sheet is hereby deleted and replaced with the following:

Base Rent with respect to Phase 2:	Period of Time	Annual Base Rent	Monthly Payment
	Phase 2 RCD End of Rent Year 1	\$2,958,207.50 <sup>2</sup>	\$246,517.29
	Rent Year 2	\$3,046,953.73	\$253,912.81
	Rent Year 3	\$3,138,362.34	\$261,530.19

	Rent Year 4	\$3,232,513.21	\$269,376.10
	Rent Year 5	\$3,329,488.60	\$277,457.38
	Rent Year 6	\$3,429,373.26	\$285,781.11
	Rent Year 7	\$3,532,254.46	\$294,354.54
	Rent Year 8	\$3,638,222.09	\$303,185.17
	Rent Year 9	\$3,747,368.76	\$312,280.73
	Rent Year 10	\$3,859,789.82	\$321,649.15
	Rent Year 11	\$3,975,583.51	\$331,298.63
	Rent Year 12	\$4,094,851.02	\$341,237.58
	Rent Year 13	\$4,217,696.55	\$351,474.71

4. Vivarium. It is understood and agreed that the provisions of the Lease relating to a vivarium (including without limitation Sections 4.4(a) and (b) thereof) shall only apply in the event Tenant elects to construct a vivarium in Phase 2 after the completion of Tenant's Fitout and the occurrence of the Phase 2 Term Commencement Date (which construction shall be performed in accordance with and subject to the terms and conditions of the Lease, including without limitation Article 11 thereof and the definition of the Permitted Use set forth in the Lease Summary Sheet). It is understood and agreed that Tenant shall not have the right to construct a vivarium in Phase 1 of the Premises.

5. ACF Elevator. Notwithstanding anything to the contrary contained in the Lease (including without limitation Section 4.4(c) and Section 4(d) of the Work Letter), Landlord and Tenant acknowledge as follows:

(a) Landlord will still install the ACF Elevator with a stop on the eighth floor of the Premises, but there will not be doors constructed to provide access thereto from the eighth floor (i.e., drywall will be installed where the ACF Elevator doors would otherwise open).

(b) If Tenant elects to construct a vivarium in Phase 2 in accordance with Section 4 above, such construction shall include the installation of a doorway providing access from Phase 2 to the ACF Elevator in substantially the location more particularly shown on the Lease Plan.

(c) Unless and until Tenant constructs a vivarium in accordance with Section 2 above, Section 4.4(c) of the Lease shall have no force and effect.

(d) Tenant shall not have the right to use the ACF Elevator (i) prior to substantial completion of Alterations to Phase 2 of the Premises to construct a vivarium, nor (ii) unless and until Landlord and Tenant execute an amendment to this Lease increasing the rentable square footage of the Premises by 589 rentable square feet, with proportionate adjustments to Base Rent, Tenants' Share and Tenant's Tax Share.

(e) The second sentence of Section 4(d) of the Work Letter is hereby deleted in its entirety.

6. Final Construction Drawings. Notwithstanding anything to the contrary contained in the Lease, Tenant shall deliver Final Construction Drawings with respect to Phase 2 on or before May 27, 2020. The Phase 2 Final Construction Drawings shall not include the construction of a vivarium.

7. Ratification. Except as amended hereby, the terms and conditions of the Lease shall remain unaffected. From and after the date hereof, all references to the Lease shall mean the Lease as amended hereby. Additionally, Tenant confirms and ratifies that, as of the date hereof and to its actual knowledge,

(a) the Lease is and remains in good standing and in full force and effect, and (b) it has no claims, counterclaims, set-offs or defenses against Landlord arising out of the Lease or the Premises or in any way relating thereto.

8. Miscellaneous. This First Amendment shall be deemed to have been executed and delivered within the Commonwealth of Massachusetts, and the rights and obligations of Landlord and Tenant hereunder shall be construed and enforced in accordance with, and governed by, the laws of the Commonwealth of Massachusetts without regard to the laws governing conflicts of laws. If any term of this First Amendment or the application thereof to any person or circumstances shall be invalid and unenforceable, the remaining provisions of this First Amendment, the application of such term to persons or circumstances other than those as to which it is invalid or unenforceable, shall not be affected. This First Amendment is binding upon and shall inure to the benefit of Landlord and Tenant and their respective successors and assigns. Each party has cooperated in the drafting and preparation of this First Amendment and, therefore, in any construction to be made of this First Amendment, the same shall not be construed against either party. In the event of litigation relating to this First Amendment, the prevailing party shall be entitled to reimbursement from the other party of its reasonable attorneys' fees and costs. This First Amendment constitutes the entire agreement of the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions, and may not be amended, waived, discharged or terminated except by a written instrument signed by all the parties hereto. A facsimile, PDF or other electronic signature on this First Amendment shall be equivalent to, and have the same force and effect as, an original signature. This First Amendment may be executed in counterparts which, taken together, shall constitute a single instrument.

[signatures on following page]

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EXECUTED as of the date first set forth above.

LANDLORD: MASSACHUSETTS INSTITUTE OF TECHNOLOGY

By: /s/ Seth D. Alexander

Name: Seth D. Alexander

Title: Authorized Signatory, President, MIT Investment Management Company and not individually

TENANT: BEAM THERAPEUTICS, INC.

By: /s/ John Evans

Name: John Evans

Title: CEO

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**SECOND AMENDMENT TO LEASE**

This Second Amendment to Lease (this “**Second Amendment**”) is made as of November 17, 2020 by and between MASSACHUSETTS INSTITUTE OF TECHNOLOGY, a Massachusetts charitable corporation with an address of c/o MIT Investment Management Company, One Broadway, Suite 09-200, Cambridge, MA 02142 (“**Landlord**”), and BEAM THERAPEUTICS, INC., a Delaware corporation with an address of 26 Lansdowne Street, 2<sup>nd</sup> Floor, Cambridge, MA 02139 (“**Tenant**”).

## WITNESSETH

WHEREAS, Landlord and Tenant are the current parties to that certain Lease dated April 24, 2019, as amended by that certain First Amendment to Lease dated as of April 14, 2020 (collectively, the “**Lease**”), pursuant to which Landlord is leasing to Tenant approximately 122,620 rentable square feet (as more particularly described in the Lease, the “**Premises**”) located on the seventh, eighth, ninth and tenth floors of the Laboratory Addition to the building located at 238 Main Street, Cambridge, MA;

WHEREAS, immediately prior to the date hereof, as a result of Landlord’s Force Majeure delays (specifically, the COVID-19 pandemic and the related construction moratorium), subject to any Tenant Delays and any further Landlord’s Force Majeure delays, the Estimated Phase 1 Delivery Date is November 24, 2021, and the Estimated Phase 2 Delivery Date is November 24, 2022;

WHEREAS, Landlord has worked with the Approved Contractor to mitigate delays caused by the existing Landlord’s Force Majeure delays and, subject to any Tenant Delays and any further Landlord’s Force Majeure delays, it is expected that (a) Phase 1 of the Premises will be delivered to Tenant in the condition required by the Lease on or before October 24, 2021, and (b) Phase 2 of the Premises will be delivered to Tenant in the condition required by the Lease on or before December 15, 2021;

WHEREAS, Landlord and Tenant have agreed to amend the Lease to accelerate the Estimated Delivery Dates to be more in line with the current construction schedule and

WHEREAS, Landlord and Tenant wish to memorialize their agreements with respect thereto.

NOW, THEREFORE, in consideration of the covenants herein reserved and contained, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. **Recitals; Capitalized Terms.** The foregoing recitals are hereby incorporated by reference. All capitalized terms not otherwise defined herein shall have the meanings ascribed to them as set forth in the Lease.
  2. **Estimated Delivery Dates.** Notwithstanding anything to the contrary contained in the Lease, from and after the date hereof, subject to any Tenant Delays and any further Landlord’s Force Majeure delays (a) the “**Estimated Phase 1 Delivery Date**” shall mean October 24, 2021; and (b) the “**Estimated Phase 2 Delivery Date**” shall mean December 15, 2021.
  3. **Ratification.** Except as amended hereby, the terms and conditions of the Lease shall remain unaffected. From and after the date hereof, all references to the Lease shall mean the Lease as amended hereby. Additionally, Tenant confirms and ratifies that, as of the date hereof and to its actual knowledge,  
(a) the Lease is and remains in good standing and in full force and effect, and (b) it has no claims, counterclaims, set-offs or defenses against Landlord arising out of the Lease or the Premises or in any way relating thereto.
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4. Miscellaneous. This Second Amendment shall be deemed to have been executed and delivered within the Commonwealth of Massachusetts, and the rights and obligations of Landlord and Tenant hereunder shall be construed and enforced in accordance with, and governed by, the laws of the Commonwealth of Massachusetts without regard to the laws governing conflicts of laws. If any term of this Second Amendment or the application thereof to any person or circumstances shall be invalid and unenforceable, the remaining provisions of this Second Amendment, the application of such term to persons or circumstances other than those as to which it is invalid or unenforceable, shall not be affected. This Second Amendment is binding upon and shall inure to the benefit of Landlord and Tenant and their respective successors and assigns. Each party has cooperated in the drafting and preparation of this Second Amendment and, therefore, in any construction to be made of this Second Amendment, the same shall not be construed against either party. In the event of litigation relating to this Second Amendment, the prevailing party shall be entitled to reimbursement from the other party of its reasonable attorneys' fees and costs. This Second Amendment constitutes the entire agreement of the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions, and may not be amended, waived, discharged or terminated except by a written instrument signed by all the parties hereto. A facsimile, PDF or other electronic signature on this Second Amendment shall be equivalent to, and have the same force and effect as, an original signature. This Second Amendment may be executed in counterparts which, taken together, shall constitute a single instrument.

[signatures on following page]

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[SIGNATURE PAGE TO SECOND AMENDMENT TO LEASE BY AND BETWEEN MASSACHUSETTS INSTITUTE OF TECHNOLOGY AND BEAM THERAPEUTICS, INC.]

EXECUTED as of the date first set forth above.

LANDLORD: MASSACHUSETTS INSTITUTE OF TECHNOLOGY

By: /s/ Seth D. Alexander

Seth D. Alexander, Authorized Signatory, and not individually

TENANT: BEAM THERAPEUTICS, INC.

By: /s/ John Evans

Name: John Evans

Title: CEO\_\_\_

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**THIRD AMENDMENT TO LEASE**

This Third Amendment to Lease (this "Third Amendment") is made as of August 24th 2021 by and between MIT 238 MAIN STREET LEASEHOLD LLC, a Massachusetts charitable corporation with an address of c/o MIT Cambridge Real Estate LLC, One Broadway, Suite 09-200, Cambridge, MA 02142 ("Landlord"), successor-in-interest to Massachusetts Institute of Technology, and BEAM THERAPEUTICS, INC., a Delaware corporation with an address of 26 Lansdowne Street, 2<sup>nd</sup> Floor, Cambridge, MA 02139 ("Tenant").

## WITNESSETH

WHEREAS, Landlord and Tenant are the current parties to that certain Lease dated April 24, 2019, as amended by that certain First Amendment to Lease dated as of April 14, 2020 and as further amended by that certain Second Amendment to Lease dated as of November 17, 2020 (collectively, the "Lease"), pursuant to which Landlord is leasing to Tenant approximately 122,620 rentable square feet (as more particularly described in the Lease, the "Original Premises") located on the seventh, eighth, ninth and tenth floors of the Laboratory Addition to the building located at 238 Main Street, Cambridge, MA;

WHEREAS, Tenant desires to lease additional premises on the sixth (6th) floor of the Laboratory Addition consisting of approximately 7,638 rentable square feet of space, including associated mechanical, ground floor lower level space (as more particularly shown on the plan attached hereto as Exhibit A, the "Expansion Space");

WHEREAS, Landlord is willing to lease the Expansion Space to Tenant on the terms and conditions hereinafter set forth; and

WHEREAS, Landlord and Tenant wish to amend the Lease on the terms and conditions hereinafter set forth.

NOW, THEREFORE, in consideration of the covenants herein reserved and contained, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant hereby agree as follows:

1. Recitals: Capitalized Terms. The foregoing recitals are hereby incorporated by reference. All capitalized terms not otherwise defined herein shall have the meanings ascribed to them as set forth in the Lease.

2. Lease of Expansion Space.

(a) Landlord hereby leases to Tenant, and Tenant hereby leases from Landlord, the Expansion Space for a term (the "ES Term") commencing on the date on which the Expansion Space is delivered to Tenant in the condition required by Section 2(b) below (the "ES Commencement Date") and ending on the last day of the Term (as it may be extended pursuant to the terms of the Lease), subject to all of the terms and conditions of the Lease (including without limitation the payment of utility charges) except as expressly set forth in this Third Amendment. From and after the ES Commencement Date, (i) the "Premises" shall be deemed to mean, for all purposes of the Lease (as amended hereby), collectively the Original Premises and the Expansion Space (comprising a total of 130,258 rentable square feet in the aggregate), and (ii) Exhibit 2A to the Lease shall be deemed to include Exhibit A to this Third Amendment.

(b) On the ES Commencement Date, Landlord shall deliver to Tenant the Expansion Space with (i) Tenant's ES Fitout (hereinafter defined) completed except for TESH Punchlist Items (hereinafter defined), as certified in writing by Tenant's architect (subject to Section 3(e) of the Work Letter (as incorporated herein pursuant to Section 3(a) below)), and (ii) Landlord's Base Building Work with respect thereto substantially complete (as defined in Section 4(b) of the Work Letter). Subject to the foregoing, Tenant acknowledges and agrees that Tenant hereby leases the Expansion Space in its "AS IS," "WHERE IS" condition and with all faults on the ES Commencement Date, without representations or warranties, express or implied, in fact or by law, of any kind, and without recourse to Landlord.

### 3. Construction.

(a) Incorporation of Work Letter. The following provisions of the Work Letter shall be incorporated herein so as to also apply to Tenant's ES Fitout: Sections 1, 2(c), 2(d), 2(g), 3(b), 3(e), 3(f), 3(h), 5(c)(ii), 5(c)(iii), 5(c)(iv), 5(c)(v), 5(d)(i), 5(d)(ii), and 5(d)(iii); provided, however, all references in such provisions to (i) "this Work Letter" shall be deemed to refer to this Section 3, (ii) "Tenant's Fitout" (including references to Tenant's Fitout by way of reference to Landlord's Work) shall be deemed to refer to Tenant's ES Fitout, (iii) "TF Punchlist" shall be deemed to refer to the TESH Punchlist, (iv) the "Execution Date" shall be deemed to refer to the date of this Third Amendment, (v) "the Final Cost Estimate" shall be deemed to refer to the Final Cost Estimate prepared with respect to the Approved ES Plans pursuant to Section 5(c) of the Work Letter (incorporated herein pursuant to this Section 3(a)), (vi) "Work Costs" shall be deemed to refer to the ES Costs, (vii) "Premises" (or any Phase thereof) shall be deemed to refer to the Expansion Space, (viii) "Estimated Delivery Date" shall be deemed to refer to the Estimated ES Delivery Date, (ix) the "Plans" (or any of the plans constituting the Plans) shall be deemed to refer to the ES Plans (or the corresponding ES Plan), and (x) the "Shell Space" (or the Shell Space Allowance) shall be deemed to refer to the ES Shell Space (or the ES Shell Space Allowance).

(b) Tenant's ES Fitout. Landlord, at Landlord's sole cost and expense (subject to Section 3(h), below), shall engage the Approved Contractor to construct all of the improvements set forth in the Final ES Plans (hereinafter defined) using new materials of the quality called for in such plans, in a good and workmanlike manner, and in accordance with all Legal Requirements. Subject to day-for-day delays on account of Landlord's Force Majeure and Tenant Delays, Landlord shall use commercially reasonable efforts to substantially complete Tenant's ES Fitout on or before January 15, 2023 (the "Estimated ES Delivery Date"). Subject to performance of the TESH Punchlist Items, Landlord will be deemed to have fully performed all of its obligations under this Section 3 upon the ES Commencement Date: provided, however, if timely notice has been given and if Landlord has the benefit of any guarantees, contract rights, or other claims against contractors, material men or architects, Landlord shall, with regard to any defects in Tenant's ES Fitout, exercise commercially reasonable efforts (which shall not require any litigation or alternative dispute resolution) to enforce such guarantees or contract rights; provided, further, Landlord shall have no such obligation with respect to any (A) defect(s) in the Final ES Plans, (B) manufacturer's defects with respect to any equipment or fixtures purchased directly by Tenant, nor (C) with respect to any defect(s) resulting from (w) misuse, (x) Tenant's breach of its maintenance and repair obligations under the Lease, (y) the negligence or willful misconduct of any Tenant Party, or (z) reasonable wear and tear.

(c) Schedule. Attached hereto as Exhibit B is the estimated schedule for design and construction phases of Tenant's ES Fitout (as the same is updated pursuant to the terms hereof, the "ES Construction Schedule"). During the course of design and construction of Tenant's ES Fitout, Landlord shall cause the ES Construction Schedule to be updated periodically to reflect the actual progress of such design and construction, as applicable, and shall cause such updates to be delivered to Tenant monthly, but such updates shall not be deemed to amend or modify any of Landlord's obligations under this Section 3.

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(d) Plans. In connection with the performance of the work necessary to prepare the Expansion Space for Tenant's occupancy and business operations ("Tenant's ES Fitout"), Tenant shall engage AHA Consulting Engineers, Inc. or AEI Affiliated Engineers as Tenant's MEP Engineer and shall engage Perkins & Will as Tenant's architect. Furthermore, in connection with Tenant's ES Fitout, Tenant shall deliver to Landlord for Landlord's approval (i) on or before October 1, 2021, an electronic copy and four (4) full sized copies of design development plans, with sufficient information and detail to accurately describe the proposed design of the Expansion Space and document the programmatic requirements for Tenant's ES Fitout (it being understood and agreed that the mechanical and electrical portions of such plans shall be suitable for purchase of subcontract bidding and contracting) (the "ES Design Development Plans"), and (ii) on or before December 15, 2021, an electronic copy and four (4) full sized copies of a fully coordinated set of architectural, structural, mechanical, electrical and plumbing engineering plans and specifications based on the approved ES Design Development Plans and in a form which is sufficiently complete to allow the Approved Contractor and subcontractors to bid on the work and to obtain all applicable permits for Tenant's ES Fitout ("Final ES Construction Drawings"). The ES Design Development Plans and the Final ES Construction Drawings are collectively referred to herein as the "ES Plans." It is understood and agreed that Tenant's ES Fitout does not include the installation of Tenant's furniture, trade fixtures or equipment, the installation of which shall be performed in accordance with Section 11 of the Lease by Tenant (as contemplated by Section 3(h) of the Work Letter (as incorporated herein pursuant to Section 3(a), above)). Landlord's approval of the ES Design Development Plans (and the Final ES Construction Drawings, provided that the Final ES Construction Drawings are consistent with the ES Design/Development Plans) shall not be unreasonably withheld, conditioned or delayed provided the ES Plans comply with the requirements to avoid aesthetic or other conflicts with the design and function of the balance of the Building and the Property; and provided, further that Landlord may withhold its approval in its sole discretion with respect to Restricted Alterations. Landlord may reasonably disapprove any iteration of any of the ES Plans based on Landlord's reasonable conclusion that one or more aspects of such ES Plans will cause an actual delay of the substantial completion of Landlord's Work and/or Tenant's ES Fitout beyond the applicable Estimated Delivery Date (it being understood that if Landlord reasonably disapproves any of the ES Plans on such basis, and Tenant determines in writing to negate such disapproval, any such actual delay of substantial completion of Landlord's Work and/or Tenant's ES Fitout shall be deemed a Tenant Delay, and Landlord shall not disapprove such ES Plans based on such potential delay). Landlord's approval is solely given for the benefit of Landlord and Tenant under this Section 3 and neither Tenant nor any third party shall have the right to rely upon Landlord's approval of the ES Plans for any other purpose whatsoever. Landlord shall not be responsible for any errors, omissions or defects contained in the ES Plans or the costs resulting therefrom. To the extent substantial completion of Tenant's ES Fitout is delayed due to errors, omissions or defects in any of the ES Plans, such delays shall be Tenant Delays. Any request for approval of the ES Plans shall be accompanied by (A) a certification from a licensed code engineer that such plans are code compliant, and (B) a certification from Landlord's MEP engineer that the ES Plans are compatible with the base building design. If Tenant timely submits drafts of the ES Plans for review and approval, Landlord shall use commercially reasonable efforts to respond to any such timely request for approval of the ES Plans within twelve (12) business days after receipt thereof: provided, however, so long as Perkins & Will is the architect for Tenant's ES Fitout, Landlord shall use commercially reasonable efforts to respond to any such timely request for approval of the ES Plans within five (5) business days after receipt thereof. Landlord shall notify Tenant in reasonable detail if any of the ES Plans are unsatisfactory or incomplete in any respect. In the event Landlord disapproves any of the ES Plans, Tenant shall revise the same to address Landlord's comments and shall submit such revised ES Plan to Landlord for approval (and such process shall be continued until such ES Plan is approved by Landlord). The iteration of the Final ES Construction Drawings that is approved by Landlord shall be referred to herein as the "Approved ES Plans." The ES Approved Plans, as they may be changed pursuant to Section 3(b) of the Work Letter (as incorporated herein pursuant to Section 3(a) above), are hereinafter referred to as the "Final ES Plans."

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(e) TESF Punchlist. Attached to the certificate of substantial completion for Tenant's ES Fitout consistent with Section 3(f) of the Work Letter (as incorporated herein pursuant to Section 3(a) above) shall be a list prepared by Tenant's architect (the "TESF Punchlist") of outstanding items (the "TESF Punchlist Items") which (i) need to be performed to complete Tenant's ES Fitout, and (ii) do not materially interfere with the use of the Expansion Space for the Permitted Use. Subject to Landlord's Force Majeure and Tenant Delays, Landlord shall, unless otherwise specified on the TESF Punchlist, endeavor to complete the TESF Punchlist Items within sixty (60) days of the date of the TESF Punchlist.

(f) ES Costs. For purposes hereof, "ES Costs" means (i) all costs incurred by Landlord in connection with or reasonably allocated to Tenant's ES Fitout without mark-up, including without limitation the costs of reviewing the ES Plans and the costs of permitting, constructing, coordinating and performing Tenant's ES Fitout, as affected by any changes made (or requested by Tenant) in accordance with Section 3(b) of the Work Letter (as incorporated herein pursuant to Section 3(a) above) and the costs of any third party construction/project manager(s) engaged by Landlord, less (ii) the Excluded ES Construction Costs (hereinafter defined). With respect to costs incurred in connection with both Landlord's Base Building Work and Tenant's ES Fitout (including without limitation police details, rubbish removal and hoisting costs), such costs shall be allocated between Landlord's Base Building Work and Tenant's ES Fitout according to the volume of work in place the prior month (or another reasonable method). Tenant's ES Fitout shall be performed on a so-called "open book" basis.

(g) ES Allowance. As an inducement to Tenant's entering into this Third Amendment, Landlord shall pay for up to One Million Six Hundred Three Thousand Nine Hundred Eighty and no/100 Dollars (\$1,603,980.00) (the "ES Allowance") of the ES Costs other than the following costs (collectively, "Excluded ES Construction Costs"), which Excluded ES Construction Costs shall be paid for by Tenant within thirty (30) days of demand from time to time during the design and/or construction phases of Tenant's ES Fitout (but in no event more often than monthly): (i) the cost of acquiring or installing any of Tenant's Property, including without limitation telecommunications and computer equipment and all associated wiring and cabling, any de-mountable decorations, artwork and partitions, signs, and trade fixtures, or (ii) any so-called "soft costs"; provided, however, notwithstanding the foregoing, up to One Hundred Sixty Thousand Three Hundred Ninety-Eight and no/100 Dollars (\$160,398.00) of the ES Allowance may be used for Tenant's architectural, engineering and consultant fees and design and permitting costs and the cost of Tenant's wiring and cabling relating to Tenant's ES Fitout. Landlord shall not charge any supervisory or management fees with respect to Tenant's ES Fitout, provided that there shall be included in ES Costs the costs of third-party review of the ES Plans and reasonable out of pocket costs of any third-party construction/project manager(s) engaged by Landlord. Tenant shall not be entitled to any unused portion of the ES Allowance. Notwithstanding anything to the contrary, if the Final ES Plans reflect that any portion of the Expansion Space will be delivered in shell condition ("ES Shell Space"), then the portion of the ES Allowance allocable to the ES Shell Space (the "ES Shell Space Allowance") shall be held and disbursed by Landlord in accordance with Sections 5(d)(i) and (ii) of the Work Letter (as incorporated herein pursuant to Section 3(a) above).

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(h) Responsibility for Costs. If the Final ES Cost Estimate discloses that the ES Costs exceed the ES Allowance (such excess, the "Excess ES Costs"), Tenant shall pay, within thirty (30) days after demand from time to time (but in no event more than monthly), Tenant's ES Proportion (hereinafter defined) of the ES Costs reflected on each requisition from Landlord, to which shall be attached invoices and/or other documentation supporting the requisition. "Tenant's ES Proportion" shall be a fraction, the numerator of which is the estimated Excess ES Costs, and the denominator of which is the estimated ES Costs. If Tenant fails to timely make any such payment in full, each day between such 30<sup>th</sup> day and the date on which Tenant makes such payment in full shall constitute a Tenant Delay. After final completion of Tenant's ES Fitout, Landlord shall prepare and submit to Tenant a final reconciliation in sufficient detail to reasonably determine actual ES Costs (including without limitation all TESH Punchlist Items) (the "Final ES Reconciliation"). Landlord shall use reasonable efforts to deliver the Final ES Reconciliation to Tenant within ninety (90) days after final completion of Tenant's ES Fitout. Within thirty (30) days after delivery of the Final ES Reconciliation, Tenant shall pay to Landlord any remaining Excess ES Costs (or Landlord shall refund to Tenant any amounts paid by Tenant in excess of the actual Excess ES Costs).

(i) Space Planning Allowance. In addition to the ES Allowance, and as a further inducement to Tenant's entering into this Third Amendment, Landlord shall, subject to this Section 3(i), provide to Tenant a special tenant improvement allowance equal to Nine Hundred Sixteen and 56/100 Dollars (\$916.56) (the "Space Planning Allowance") to be used by Tenant solely for design and architectural costs incurred by Tenant for space planning the Expansion Space. Provided there is no Event of Default or event which, with the passage of time and/or the giving of notice would constitute an Event of Default, Landlord shall pay the Space Planning Allowance to Tenant within thirty (30) days after the later to occur of (a) Landlord's receipt of the draft ES Design Development Plans, and (b) Landlord's receipt of a reasonably detailed invoice therefor, which invoice must be delivered to Landlord on or before the date which is sixty (60) days after the ES Commencement Date: provided, however, that if Tenant cures any default prior to the expiration of applicable cure periods set forth in Article 20 of the Lease, then Landlord's obligation to pay the Space Planning Allowance shall be reinstated. Tenant shall not be entitled to any unused portion of the Space Planning Allowance.

4. Base Rent. Notwithstanding anything to the contrary, commencing on the ES Rent Commencement Date, Base Rent during the Initial Term with respect to the Expansion Space shall be paid in the following amounts, prorated for any partial months, and otherwise in accordance with the terms of the Lease:

<u>ES Rent Year</u>	<u>Annual Base Rent</u>	<u>Monthly</u>	
		<u>Installment</u>	<u>Per RSF</u>
1	\$863,094.00	\$71,924.50	\$113.00
2	\$888,986.82	\$74,082.24	\$116.39
3	\$915,656.42	\$76,304.70	\$119.88
4	\$943,126.12	\$78,593.84	\$123.48
5	\$971,419.90	\$80,951.66	\$127.18
6	\$1,000,562.50	\$83,380.21	\$131.00
7	\$1,030,579.37	\$85,881.61	\$134.93
8	\$1,061,496.75	\$88,458.06	\$138.98
9	\$1,093,341.66	\$91,111.80	\$143.15
10	\$1,126,141.91	\$93,845.16	\$147.44
11	\$1,159,926.16	\$96,660.51	\$151.86

The "ES Rent Commencement Date" shall mean the ES Commencement Date, subject to acceleration on a day for day basis for each day of Tenant Delay (if any). Base Rent with respect to the Expansion Space during the Extension Terms, if any, shall be determined in accordance with Section 1.2 of the Lease. Base Rent with respect to the Original Premises shall be paid in the amounts set forth in the Lease.

5. Letter of Credit.

(a) Landlord and Tenant acknowledge and agree that Landlord is holding a letter of credit in the amount of \$11,832,830.00 in accordance with Section 7 of the Lease (the "Existing Letter of Credit"). Within ten (10) business days of the Phase 1 Rent Commencement Date, Tenant shall deliver to Landlord either (i) an additional irrevocable letter of credit which shall be in the amount of Eight Hundred Sixty Three Thousand Ninety-Four and no/100 Dollars (\$863,094.00) and otherwise meeting the requirements of Section 7 of the Lease, or (ii) an amendment to the Existing Letter of Credit increasing the face amount thereof by Eight Hundred Sixty-Three Thousand Ninety-Four and no/100 Dollars (\$863,094.00). From and after the delivery thereof, all references in the Lease to the "Letter of Credit" shall mean, collectively, the Existing Letter of Credit together with such additional letter of credit, or such amendment, as applicable.

(b) So long as Tenant complies with its obligations under Section 5(a) above, Section 7.1(a) of the Lease shall be deleted in its entirety and replaced with the following: "If no Event of Default has occurred and no event has occurred which, with the passage of time and/or the giving of notice, would constitute an Event of Default and further provided that there is no material adverse change in Tenant's tangible net worth (as defined in Section 13.4 below) as verified by Landlord based upon a certificate from Tenant's chief financial officer and audited financials, then the face amount of the Letter of Credit may be reduced by Tenant to (a) Nine Million Seven Hundred Thirty-Seven Thousand Seven Hundred Sixteen and 53/100 Dollars (\$9,737,716.53) on or after the Phase 1 Rent Commencement Date, (b) Six Million Seven Hundred Seventy-Nine Thousand Five Hundred Nine and 02/100 Dollars (\$6,779,509.02) on or after the commencement of Rent Year 2, (c) Four Million Five Hundred Ninety-One Thousand Five Hundred Ninety-Seven and 18/100 Dollars (\$4,591,597.18) on or after the commencement of Rent Year 3, (d) Four Million Three Hundred Seventy-Five Thousand Eight Hundred Twenty-Three and 68/100 Dollars (\$4,375,823.68) on or after the commencement of ES Rent Year 2, and (e) Four Million Two Hundred Thirty-One Thousand Nine Hundred Seventy-Four and 68/100 Dollars (\$4,231,974.68) on or after the commencement of ES Rent Year 3; it being understood and agreed that if Tenant cures any default prior to the expiration of the notice and/or cure periods set forth in Section 20.1 below, or Tenant thereafter demonstrates that there is no longer a material adverse change in Tenant's tangible net worth, Tenant shall then be entitled to obtain a Letter of Credit in the reduced face amount in accordance with this Section 7.1(a). Landlord shall, at no cost to Landlord, cooperate with Tenant and the issuer of the Letter of Credit in connection with the amendment of the Letter of Credit to effectuate such reduction. Tenant hereby certifies that Tenant's tangible net worth as of February 28, 2019 was at least One Hundred Fifty Million Dollars (\$150,000,000.00).

6. Parking. Commencing on the ES Commencement Date, the number of Parking Passes to which Tenant will be entitled shall be calculated based on the rentable square footage of the entire Premises (i.e., the Original Premises and the Expansion Space).

7. Plan of Chemical Storage. Effective as of the date of this Third Amendment, the plan of the ground floor space associated with the Original Premises (which plan is labelled "Kendall Site 3 Chemical Storage - Secured Space" and is attached as the 5<sup>th</sup> page of Exhibit 2A to the Lease) is hereby deleted and replaced with the plan attached hereto as Exhibit A-1. Exhibit A-1 attached hereto depicts the ground floor space associated with both the Original Premises and the Expansion Space.

8. Hazardous Materials Management Plan. In furtherance of Tenant's obligations under Article 17 and Section 18.1 of the Lease, Tenant will comply with the Building's Hazardous Materials Management Plan (as the same may be amended from time to time, the "HMMP") with respect to the safe handling, transportation, storage and removal of Hazardous Materials.

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9. Broker. Landlord and Tenant each warrants and represents that it has dealt with no broker in connection with this Third Amendment other than CBRE ("Broker"). Landlord and Tenant each agrees to defend, indemnify and save the other harmless from and against any Claims arising as a result of its breach of the foregoing representation and warranty. Landlord shall be solely responsible for the payment of any brokerage commissions to Broker.

10. Ratification. Except as amended hereby, the terms and conditions of the Lease shall remain unaffected. From and after the date hereof, all references to the Lease shall mean the Lease as amended hereby. Tenant confirms and ratifies that, as of the date hereof and to its actual knowledge, (a) the Lease is and remains in good standing and in full force and effect, and (b) it has no claims, counterclaims, set-offs or defenses against Landlord arising out of the Lease or the Premises or in anyway relating thereto.

11. Miscellaneous. This Third Amendment shall be deemed to have been executed and delivered within the Commonwealth of Massachusetts, and the rights and obligations of Landlord and Tenant hereunder shall be construed and enforced in accordance with, and governed by, the laws of the Commonwealth of Massachusetts without regard to the laws governing conflicts of laws. If any term of this Third Amendment or the application thereof to any person or circumstances shall be invalid and unenforceable, the remaining provisions of this Third Amendment, the application of such term to persons or circumstances other than those as to which it is invalid or unenforceable, shall not be affected. This Third Amendment is binding upon and shall inure to the benefit of Landlord and Tenant and their respective successors and assigns. Each party has cooperated in the drafting and preparation of this Third Amendment and, therefore, in any construction to be made of this Third Amendment, the same shall not be construed against either party. In the event of litigation relating to this Third Amendment, the prevailing party shall be entitled to reimbursement from the other party of its reasonable attorneys' fees and costs. This Third Amendment constitutes the entire agreement of the parties with respect to the subject matter hereof and supersedes all prior and contemporaneous oral and written agreements and discussions, and may not be amended, waived, discharged or terminated except by a written instrument signed by all the parties hereto. A facsimile, PDF or other electronic signature on this Third Amendment shall be equivalent to, and have the same force and effect as, an original signature. This Third Amendment may be executed in counterparts which, taken together, shall constitute a single instrument.

[SIGNATURES ON FOLLOWING PAGE]

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[SIGNATURE PAGE TO THIRD AMENDMENT TO LEASE BY AND BETWEEN MIT 238 MAIN STREET  
LEASEHOLD LLC AND BEAM THERAPEUTICS, INC.]

EXECUTED as of the date first set forth above.

LANDLORD: MIT 238 MAIN STREET LEASEHOLD LLC

By: MIT Cambridge Real Estate LLC, its manager

By: /s/ Seth D. Alexander

Seth D. Alexander, President, and not individually

TENANT: BEAM THERAPEUTICS, INC.

By: /s/ John Evans

Name: John Evans

Title: CEO

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**Subsidiaries of Beam Therapeutics Inc.**

<b>Entity</b>	<b>State or other Jurisdiction of Incorporation or Organization</b>
Beam Therapeutics Securities Corporation	Massachusetts
Guide Therapeutics, LLC	Delaware

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**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We consent to the incorporation by reference in Registration Statement Nos. 333-236582 and 333-254378 on Form S-8, and Registration Statement Nos. 333-256962 and 333-254946 on Form S-3 of our reports dated February 28, 2022, relating to the financial statements of Beam Therapeutics Inc. and subsidiaries, and the effectiveness of Beam Therapeutics Inc. and subsidiaries' internal control over financial reporting, appearing in this Annual Report on Form 10-K for the year ended December 31, 2021.

/s/ Deloitte & Touche LLP

Boston, Massachusetts  
February 28, 2022

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**CERTIFICATION PURSUANT TO  
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,  
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, John Evans, certify that:

1. I have reviewed this Annual Report on Form 10-K of Beam Therapeutics Inc.;
  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(s) 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
    - (c) 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
    - (d) 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(s) 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):
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- (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: February 28, 2022

By: /s/ John Evans  
**John Evans**  
**Chief Executive Officer**  
**(Principal executive officer)**

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**CERTIFICATION PURSUANT TO  
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,  
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Terry-Ann Burrell, certify that:

1. I have reviewed this Annual Report on Form 10-K of Beam Therapeutics Inc.;
  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(s) 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;
    - (c) 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
    - (d) 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(s) 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
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- (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: February 28, 2022

By: /s/ Terry-Ann Burrell  
**Terry-Ann Burrell**  
**Chief Financial Officer**  
**(Principal financial and accounting officer)**

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**CERTIFICATION PURSUANT TO  
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO  
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with this Annual Report of Beam Therapeutics Inc. (the "Company") on Form 10-K for the period ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

- (1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 28, 2022

By: /s/ John Evans

**John Evans**  
**Chief Executive Officer**  
**(Principal executive officer)**

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**CERTIFICATION PURSUANT TO  
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO  
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with this Annual Report of Beam Therapeutics Inc. (the "Company") on Form 10-K for the period ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

- (1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- (2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 28, 2022

By: /s/ Terry-Ann Burrell

**Terry-Ann Burrell**  
**Chief Financial Officer**  
**(Principal financial and accounting officer)**

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