Intellia Therapeutics, Inc.
Form 10-K
March 14, 2018

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, 2017

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 001-37766

INTELLIA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	36-4785571
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
40 Erie Street, Suite 130 Cambridge, Massachusetts	02139
(Address of principal executive offices)	(Zip Code)

(857) 285-6200

(Registrant’s telephone number, including area code)

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

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

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

None

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

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

Large accelerated filer		Accelerated filer
Non-accelerated filer	(Do not check if a smaller reporting company)	Smaller reporting company
Emerging growth company		

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

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

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $235.3 million as of June 30, 2017 (based on a closing price of $16.00 per share as quoted by the Nasdaq Global Market as of such date). In determining the market value of non-affiliate common stock, shares of the registrant's

common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The registrant had 42,387,435 shares of Common Stock, $0.0001 par value per share, outstanding as of February 28, 2018.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2018 annual meeting of shareholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2017. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

Intellia Therapeutics, Inc.

Annual Report on Form 10-K for the Fiscal Year Ended December 31, 2017

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Forward-looking Information

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

- the initiation, timing, progress and results of our research and development programs and future preclinical and clinical studies;
- our ability to apply a risk-mitigated strategy to efficiently discover and develop product candidates, including by applying learnings from one program to other programs;
- our ability to create or maintain a pipeline of product candidates;
- our ability to manufacture or obtain material for our product candidates;
- our ability to advance any product candidates into, and successfully complete, clinical studies;
- our ability to advance our therapeutic delivery capabilities;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- our ability to operate, including commercializing products, without infringing the proprietary rights of others;
- the issuance of regulatory guidance regarding preclinical and clinical studies for genome editing products;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- the pricing and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- estimates of our expenses, future revenues, capital requirements and our needs for additional financing;
- the potential benefits of strategic collaboration agreements and our ability to enter into strategic arrangements;
- our ability to maintain and establish collaborations and licenses or obtain additional funding;
- our financial performance;
- developments relating to our competitors and our industry; and
- other risks and uncertainties, including those listed under the caption "Risk Factors."

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

PART I

Item 1. Business

Overview

We are a leading genome editing company focused on the development of proprietary, curative therapeutics utilizing a biological tool known as CRISPR/Cas9. We believe that the CRISPR/Cas9 technology has the potential to transform medicine by permanently editing disease-associated genes or genetic material in the human body with a single treatment course, and via cell therapies that can replace a patient's diseased cells or better target cancer and immunological diseases using engineered immune cells. We intend to leverage our leading scientific expertise, clinical development experience and intellectual property (IP) position to unlock broad therapeutic applications of CRISPR/Cas9 genome editing and develop a potential new class of therapeutic products.

In 2012, one of our co-founders and current scientific advisors, Dr. Jennifer Doudna, and her colleagues published a paper in the journal Science describing the use of CRISPR/Cas9 as a genome editing tool. Genome editing is the precise and targeted modification of the genetic material of cells or viruses. Since the publication of Dr. Doudna's landmark paper, thousands of research papers have been published on the CRISPR/Cas9 technology. The CRISPR/Cas9 system offers a revolutionary approach for therapeutic development due to its broad potential to precisely edit the genome. This system can be used to make three general types of edits: knockouts, repairs and insertions. Each of these editing strategies takes advantage of naturally-occurring biological mechanisms to effect the desired genetic alteration. By addressing the underlying cause of the disease, this approach has the potential to provide curative therapeutic options for patients with genetically-based diseases.

We plan to use the CRISPR/Cas9 system across two broad areas: in vivo applications, in which CRISPR/Cas9 therapeutic products are delivered directly to target cells within the body; and ex vivo (outside the body) applications, in which human cells are modified or repaired using CRISPR/Cas9, and the edited cells are administered to the patient to replace the patient's abnormal cells, to target cancer cells or to regulate abnormal immune function. Our in vivo pipeline includes proprietary programs targeting genetic diseases including transthyretin amyloidosis (ATTR), which we are co-developing with Regeneron Pharmaceuticals, Inc. (Regeneron), alpha-1 antitrypsin deficiency (AATD) and inborn errors of metabolism (IEMs) such as primary hyperoxaluria (PH-1), and infectious diseases such as chronic hepatitis B infection (HBV). Our ex vivo pipeline consists of two separate efforts: 1) a set of proprietary programs within our internal eXtellia division focused on developing engineered cell therapies to treat various oncological and autoimmune diseases, and 2) partnered programs developed in collaboration with Novartis Institutes for BioMedical Research, Inc. (Novartis), focused on chimeric antigen receptor T cells (CAR-T cells) and hematopoietic stem cells (HSCs), the stem cells from which all of the various types of blood cells originate.

The following table illustrates our current discovery programs and opportunities as of February 28, 2018:

In September 2017, we presented data from our completed long-term, 52-week, durability mouse study, demonstrating in vivo genome editing following a single, intravenous administration of CRISPR/Cas9. With a single dose, we achieved and maintained an approximately 97 percent reduction in serum TTR protein levels through 12 months. This TTR reduction was accomplished by approximately 70 percent sustained editing at the target DNA site in the liver. This study confirmed that our lipid nanoparticle (LNP) system is transiently present with 99 percent clearance of messenger RNA (mRNA) within 10 hours and of single guide RNA (sgRNA) within 72 hours in the liver. The treatment was well-tolerated at the time of administration and no adverse events were noted throughout the 52-weeks of follow up. These mouse durability results followed our presentation in August 2017 of initial data from rat studies demonstrating in vivo genome editing after a single, intravenous administration of CRISPR/Cas9. In our August 2017 presentation, we reported that, using our LNP system in rats, we had observed up to 91 percent reduction in serum TTR protein levels and up to 66 percent editing at the target DNA site in the subject animals.

In October 2017, we released interim top-line data regarding our in vivo non-human primate (NHP) exploratory pre-clinical studies. Specifically, based on preliminary studies currently at varying points of progress, liver genome editing rates using CRISPR/Cas9 delivered via our proprietary LNP system have ranged from 0.10 percent up to 32.0 percent after a single dose with various exploratory NHP guide RNAs (gRNA), LNP formulations and dosing regimens as well as with exploratory human cross-reactive gRNAs. In NHPs redosed with a subsequent application of our LNP formulations, we observed further editing that surpassed those levels achieved after a single dose, with multiple animals achieving a total of over 20 percent liver genome editing after a second dose.

These NHP results were similar to the results we observed in our initial rodent studies. We are conducting further improvements of our delivery system and proceeding to human guide selection. We expect to achieve higher levels of editing and reductions in serum levels of TTR protein that we achieved when we optimized the delivery system and CRISPR/Cas9 cargo used in our rodent models. We expect to begin Investigational New Drug (IND)-enabling activities for a human therapeutic as soon as mid-2018.

To date, in both single and repeat dose experiments, our proprietary LNP delivery system has been well-tolerated with both NHP-specific gRNA and exploratory human cross-reactive gRNAs, as assessed by gross observation of the animals, clinical chemistry, hematology, and cytokine and complement levels. We are also encouraged by the reduction in serum TTR protein levels shown to date in animals with the highest levels of editing. We are conducting additional studies in multiple animal models to maximize editing rates through repeat dosing and formulation improvements.

In October 2017, we presented data from an in vivo mouse study showing, after a single intracerebral injection, delivery to the brain of one of our proprietary LNP formulations as demonstrated by the expression of tdTomato protein. Additionally, we presented data from another in vivo mouse study showing gene editing in brain tissue following single intracerebral injections of several proprietary LNP formulations. Editing was assessed under various dosing regimens with six different proprietary LNP formulations following a single intracerebral injection targeting the striatum and cerebellum. Under these various conditions, editing levels from less than 1% up to 28% were achieved in the striatal and cerebellar tissue. The injections were well tolerated and the mice did not display any behavioral changes post dosing.

In December 2017, our collaborator Novartis presented initial data from our research collaboration on genome-edited human hematopoietic stem cells. These data showed successful ex vivo editing of the erythroid specific enhancer region of BCL11A, a gene associated with ameliorating sickle cell disease, and the ability of these cells to stably engraft in mice while maintaining their desired properties. Specifically, the data showed that approximately 80-95 percent target site modification in human hematopoietic stem and progenitor CD34+ cells was achieved following electroporation of ribonucleoprotein (RNP) composed of Cas9 and a gRNA, selected for efficacy and potency. In addition, we demonstrated an approximately 40 percent reduction in BCL11A mRNA with a corresponding two-fold increase in -globin transcript and 30-40 percent more fetal hemoglobin-positive cells above background. Editing of CD34+ cells from patient donors resulted in similar decreases in BCL11A mRNA and increases in -globin transcript. We also showed engraftment over 16 weeks following transplantation of edited human bone marrow CD34+ cells into immune compromised mice, while maintaining editing levels in engrafted cells. We did not observe any off-target events in CD34+ cells edited with the selected gRNA, as measured by targeted next generation sequencing of sites identified through in silico prediction and based on an unbiased, genome-wide, oligo-insertion detection method.

We believe our product focus, therapeutic discovery and development strength, delivery expertise and intellectual property portfolio make us well-positioned to translate the potential of the CRISPR/Cas9 system into clinically meaningful genome editing-based therapeutics. To maximize our opportunity to rapidly develop clinically successful products, we are applying a risk-mitigating approach with our initial indications and programs. Our approach is defined by four primary criteria: (i) the type of edit—knockout, repair or insertion; (ii) the delivery modality for in vivo and ex vivo applications; (iii) the presence of established therapeutic endpoints; and (iv) the potential for the CRISPR/Cas9 system to provide therapeutic benefits when compared to existing therapeutic modalities. Our current in vivo programs focus on diseases attributable to genes expressed in the liver that have significant unmet medical needs – transthyretin amyloidosis, which we are co-developing with Regeneron, alpha-1 antitrypsin deficiency, primary hyperoxaluria and chronic hepatitis B infection – and our ex vivo programs are focused on applications of the technology in CAR-T cell and HSC, product candidates which are selectively partnered with our collaborator Novartis, and other engineered cell therapies to treat various oncological and autoimmune diseases that we are developing independently.

These selection criteria position us to build a diversified pipeline, in which we are not reliant on any single delivery technology or editing approach for success. In addition, we believe we can apply the learnings from these indications and programs to inform our selection of subsequent indications and targets of interest. We believe this approach serves to increase our probabilities of success in the indications for our current programs, generate insights that will accelerate the development of additional therapeutic products and broaden the opportunity for potential strategic alliances.

Delivery plays a key role in our in vivo therapeutic approach. We have shown in animal models that LNP delivery technology, which involves encapsulating therapeutic agents into microscopic lipid droplets, can systemically deliver CRISPR/Cas9 components to the liver, our initial organ of focus for in vivo applications. We have also successfully delivered CRISPR/Cas9 components to the brain in animal models using direct injection of LNPs. With our team's

expertise with LNP delivery technology, we expect to translate the LNPs in our preclinical development to clinical development in humans. In parallel, we are exploring additional in vivo delivery vehicles, including viral delivery vectors, which are viruses engineered to carry non-viral nucleic acids to patients' cells, which we believe may assist us in treating genetic disease in other organs.

To explore the scope of gene edits with the CRISPR/Cas9 system, we have chosen four in vivo liver indications employing different editing strategies:

- ATTR program, which utilizes a gene knockout strategy;
- AATD program, which can utilize gene knockout, insertion or repair strategies;
- PH-1, our lead IEM program, which can utilize a gene knockout strategy or targeted DNA insertion; and
- HBV program, which utilizes a knockout strategy to target covalently closed circular DNA (cccDNA).

In addition to giving us four potential product opportunities, each of these programs will provide us with learnings that we intend to translate to a broader set of disease indications requiring the same types of edits in the liver and other organs.

Our partnered ex vivo programs in CAR-T cell and HSC applications are being developed with Novartis, where we retain the right to develop and commercialize rights to certain HSC programs. In CAR-T cell therapy, naturally-occurring immune cells, specifically T cells, are removed from a patient's body and modified ex vivo by inserting a chimeric antigen receptor (CAR) to selectively target cancer cells by activating an immune response against them. The CAR is an engineered fusion protein expressed on a cell's surface with an antibody-based portion that can recognize certain markers on other cells, such as cancer cells, and a signaling portion inside the cell that can deliver the desired signals when the antibody portion binds its markers. We believe CRISPR/Cas9 can further enhance CAR-T cells by, for example, generating a universal donor CAR-T cell or modifying genes that regulate T cell behavior to increase the therapeutic potential of a CAR-T cell therapy. In the HSC programs, we can apply CRISPR/Cas9 to correct defective proteins in HSCs of a given patient for the potential treatment of blood disorders or primary immune deficiencies. In additional applications, normal HSCs may be engineered ex vivo using CRISPR/Cas9 to produce cells expressing a therapeutic protein, and the cells are then returned to patients in need of that protein.

eXtellia is exploring the application of CRISPR/Cas9 gene editing in the fields of immuno-oncology beyond CAR-T cells, as well as applications of cell therapy in autoimmune and inflammatory diseases. Current focus is on developing products based on immune cells for which we retain proprietary rights, such as T cell receptor (TCR)-engineered T cells for immuno-oncology applications, engineered T regulatory cells (Tregs) for autoimmune disorders and other cell types such as engineered induced pluripotent stem cells. Our ex vivo delivery approach is a clinically proven delivery method called electroporation, an electrical charge-based technique for delivering molecules into cells, which has been used in advanced clinical studies. In parallel, we are considering other delivery methods for ex vivo introduction of biological material to cells, which may provide advantages in delivery efficiency or cell viability.

We believe our focused approach to selecting our initial and current in vivo and ex vivo programs positions us to build a pipeline across a range of indications and generate a wealth of data for opening up the potential therapeutic applications of the CRISPR/Cas9 technology across a broad range of diseases. Our collaboration and intellectual property strategies focus on leveraging existing third-party expertise in therapeutic research, preclinical and clinical development, regulatory affairs, manufacturing and commercialization, while also enhancing our industry-leading access to evolving genome editing technology, potential new therapeutic targets and delivery vehicles. Through our product research and development programs, we believe we can apply CRISPR/Cas9 technology to improve the lives of patients with significant unmet medical needs.

Strategy

Our goal is to build a fully integrated, product-driven biotechnology company, focused on developing and commercializing curative CRISPR/Cas9-based therapeutics. Our approach to advancing the broad potential of genome editing includes plans to:

Focus on Indications that Enable Us to Fully Develop the Potential of the CRISPR/Cas9 System. To maximize our opportunity to rapidly develop clinically successful products, we have applied a risk-mitigated approach to selecting indications with significant unmet medical needs based on four primary criteria:

- the type of edit: knockout, repair or insertion;
- the delivery modality for in vivo and ex vivo applications;
- the presence of established therapeutic endpoints; and
- the potential for the CRISPR/Cas9 system to provide therapeutic benefits when compared to existing therapeutic options.

We believe these selection criteria position us to build a diversified pipeline, in which we are not reliant on any single delivery technology or editing approach for success. In addition, we believe we can apply the learnings from our current programs to inform our selection of additional indications and targets of interest. We are also exploring ways to identify potential new therapeutic targets suitable for modulation with the CRISPR/Cas9 technology. We believe this approach serves to increase the probabilities of success in our initial indications, generate insights that will accelerate the development of additional therapeutic products and broaden the opportunity for potential strategic alliances.

Aggressively Pursue In Vivo Liver Indications to Develop Therapeutics Rapidly with Existing Delivery Technology. For our in vivo indications, we selected well-validated targets in diseases with significant unmet medical needs where there are predictive biomarkers, or measurable indicators of a biological condition or state, with strong disease correlation and where the CRISPR/Cas9 technology and delivery tools existing today could be applied towards developing a novel therapeutic. Our initial in vivo pipeline opportunities target diseases of the liver, which we believe we can develop using our existing LNP delivery technology. Among the first in vivo indications that we are evaluating are ATTR, AATD, PH-1, and HBV.

Actively Develop and Expand Ex Vivo Therapeutic Programs. Through eXtellia we are independently researching and developing proprietary engineered cell therapies to treat various oncological and autoimmune diseases, for example using TCR-engineered T cells for immuno-oncology applications, engineered Tregs for autoimmune disorders and other cell types such as engineered induced pluripotent stem cells. Further, in collaboration with Novartis, we are pursuing CAR-T cell and HSC programs. We believe that our work in CAR-T cells and HSCs help guide us in building our proprietary ex vivo portfolio.

Continue to Leverage Strategic Partnerships to Accelerate Clinical Development. We view strategic partnerships as important drivers for accelerating the achievement of our goal of rapidly developing curative therapies. The potential application of CRISPR/Cas9 is extremely broad, and we plan to continue to identify partners who can contribute meaningful resources and insights to our programs and allow us to more rapidly bring scientific innovation to a broader patient population. Our partnership focusing on CAR-T cells with Novartis, an industry leader with one of the most advanced clinical and commercial CAR-T cell programs, our partnership on in vivo liver indications with Regeneron, a leader in genetics-driven drug discovery and development, and our research collaboration initiated in 2017 on engineered T cell therapies with Ospedale San Raffaele, a leading European research-university hospital, exemplify this strategy.

Grow Our Leadership Position in the Field of Genome Editing. We are committed to broadening our capabilities to remain at the cutting edge of genome editing research. We will continue to invest internally in developing our platform capabilities, including innovative delivery modalities, technologies and tools to advance our therapeutic programs. We will also systematically explore accessing external technologies or opportunities to enhance our leadership position in developing innovative therapeutics.

Our Platform

An integral part of developing our therapeutic product candidates and exploring additional potential applications of CRISPR/Cas9 to future indications includes building and improving on various proprietary and in-licensed aspects of our technology platform. We continue to develop robust, high volume (high-throughput) capabilities centering around CRISPR/Cas9 components, editing strategies and delivery methods that we believe will provide us with a competitive advantage in creating successful therapeutic product candidates.

Informatics

We have built a high-throughput, scalable data processing and analysis, or informatics, infrastructure to support various aspects of our platform, including guide ribonucleic acid (RNA) selection and analysis of on- and off-target editing in cells. Depending on the desired editing strategy, we use our proprietary bioinformatics methods to design candidate guides and select those that we believe are more likely to be highly specific and have high cutting efficiency. As we grow our experimental data set, we continue to incorporate guide performance into our algorithms to improve their predictive power.

Guide RNA Qualification

As part of the process to identify guide RNAs for potential development candidates, we screen numerous guide RNAs for their ability to generate the required edit at the genomic site of interest, called on-target activity, as well as any propensity to generate unwanted events at other sites in the genome, also known as off-target activity. To evaluate on-target activity, we use high-throughput sequencing methods to analyze the genomes of edited cells, allowing us to assess overall editing efficiency and to examine the nature of the editing events, such as specific insertions or deletions.

For guide RNAs selected through our primary on-target screens, we perform a variety of analyses to look for possible off-target editing events, including bioinformatic predictions and experimental methods. Part of our approach involves identifying candidates with no or few off-target sites based on experimental measurements of genome-wide DNA breaks, as well as targeted sequencing of such candidate sites to evaluate actual off-target editing events in relevant cell types. We continue to optimize our guide RNA qualification capability over time by increasing our throughput, improving our off-target activity detection accuracy and increasing our bioinformatics predictive accuracy.

Guide RNA format

CRISPR/Cas9 systems can function with guide RNAs having a variety of modifications, such as changes to the physical guide RNA structure or chemical modifications of nucleotides. As part of our development of CRISPR/Cas9 therapeutics, we are engineering modified guide RNAs to, for example, improve editing efficiency and targeting, as well as to reduce the likelihood of an immune response. We believe our work in this area will allow us to develop the most appropriate guides for therapeutic applications.

Nuclease

Our current preferred Cas9 protein is derived from a type of bacteria called S. pyogenes (Spy), which is the Cas9 used in the vast majority of published CRISPR/Cas9 literature to date. As part of the therapeutic development process, we are adapting and engineering Spy Cas9 with the goal of improving its specificity, activity and manufacturability. In addition, we are exploring other naturally-occurring Cas9 proteins and nucleases from other organisms, which may differ from Spy Cas9 in aspects such as specificity, size or mechanism of DNA cut. We are pursuing these alternative Cas9 forms and other nucleases through ongoing internal work, by collaborating with our existing partners and

scientific founders and by investigating in-licensing opportunities. We are also investigating targeted modifications of Cas9 that can modulate DNA activity by mechanisms other than cleavage. We believe that different therapeutic applications may be best addressed using different forms of Cas9 or other nucleases, depending on the target cell or tissue of interest, the delivery method and the desired type of edit.

Cas9 Edit type

While knockout edits can be made using solely a Cas9 protein and guide RNA, repair and insertion edits additionally require a template nucleic acid that contains the desired corrected or inserted sequence. The way in which the template is provided depends on the delivery modality. For example, for ex vivo applications, the DNA template may be delivered by electroporation in combination with a Cas9-guide RNA complex. We are also investigating various in vivo strategies for delivering repair and insertion templates, such as delivery by LNPs or by viral vectors. Further, we are developing methods to selectively promote template-based repair or insertion mechanisms in cells, as opposed to non-template-based repair that otherwise may generate knockout edits.

In vivo delivery

We are focusing our initial in vivo applications in the liver, with delivery of CRISPR/Cas9 components by LNPs.

LNPs encapsulate the therapeutic material, providing it with stability, targeted delivery capabilities, improved pharmacologic properties and controlled circulation time, allowing for transient expression of Cas9. We see multiple advantages of using LNPs as our initial in vivo delivery vehicle, particularly as optimized by us for delivery of the CRISPR/Cas9 system or its components. Certain LNPs have demonstrated efficacy, safety and favorable tolerability and are currently used as a delivery system for therapeutic small interfering RNA (siRNA) as well as therapeutic mRNA. mRNA is RNA that encodes proteins, while siRNA is RNA that can interfere with the function of mRNA. There are currently several LNP/siRNA programs of other companies in the clinic, with the most advanced having successfully completed Phase III development, leading to a New Drug Application (NDA) filing. LNP delivery of CRISPR/Cas9-based therapies, where potentially only one or few treatment courses are needed, has the potential to show a more favorable safety profile when compared to therapeutic modalities like siRNAs where chronic dosing is needed. Additionally, LNPs are chemically well-defined and have a completely synthetic route of manufacture, which permits greater scalability. We are currently advancing our programs using a set of biodegradable, well-tolerated lipids, which are based on lipids originally developed by Novartis and in-licensed for use with CRISPR/Cas9 products. To date, we have successfully demonstrated in vivo editing in various animal models, including in mouse, rat and non-human primate livers, with a single dose of systemically delivered LNPs based on these lipids. We have also shown successful delivery and editing in mouse brain using CRISPR/Cas9 delivered by direct injection of one of our proprietary LNP formulations. The injections were well tolerated and the mice did not display any behavioral changes.

With our team's expertise in LNP delivery technology, we expect to be able to translate the LNPs that we are using for our preclinical evaluation to clinical development in humans. In addition, we are exploring options for incorporating Cas9 into therapeutic products in multiple formats. For example, Cas9 can be delivered in its protein form or could be delivered as a nucleic acid, such as an mRNA. For delivery of Cas9 mRNA, we are also investigating modifications that may improve expression and stability, as well as reduce the potential for an immune response. We plan to continue to further improve on LNP formats for a variety of CRISPR/Cas9 therapeutic components, including templates for repair and insertion edits. In parallel, we are exploring additional delivery vehicles, including synthetic particles and viral vectors, that we believe will allow us to target the central nervous system, eye, muscle and other organs.

Ex vivo delivery

Cellular therapies are based on the administration of engineered human cells that are modified to provide or restore necessary functions in the cells of patients, or to target and eliminate cells with harmful attributes, such as cancer cells. The cells to be modified ex vivo can come from the individual patient (autologous source) or from another individual (allogeneic source), and the modification takes place ex vivo. We use the CRISPR/Cas9 system to perform

the modification, and deliver the system using a clinically proven method called electroporation, an electrical charge-based technique for delivering molecules into cells. In parallel, we are exploring other delivery methods for ex vivo introduction of biological material to cells, which may provide advantages such as delivery efficiency. In human cells, we have been able to achieve relatively high editing rates, including rates greater than 90%, of both copies of a single gene (bi-allelic editing), while preserving cell viability.

We have also simultaneously targeted multiple genes in an ex vivo setting and achieved high bi-allelic editing rates for both genes, demonstrating what we believe to be therapeutically relevant editing of multiple genes simultaneously (multiplex editing). The ability to achieve multiplex editing may be critical in targeting certain diseases.

Our Pipeline

To accelerate the development and commercialization of CRISPR/Cas9-based products in multiple therapeutic areas, we are targeting various indications using in vivo and ex vivo approaches to demonstrate proof-of-concept of the various facets of our technology, including the type of edit and CRISPR/Cas9 selectivity and efficiency. We believe that the learnings we gain from each indication will pave the way for rapid expansion of our pipeline by allowing us to target subsequent indications that use the same or analogous delivery vehicles, guide structures and types of edits.

We believe that effective delivery methods will be important for the clinical success of the CRISPR/Cas9 system. Our approach is to undertake a parallel effort on both in vivo and ex vivo delivery that leverages nearly two decades of research and development in nucleic acid therapeutics and capitalizes on currently available, clinically and preclinically validated technologies, while developing next-generation delivery methods optimized for the CRISPR/Cas9 system.

In Vivo Pipeline

Our initial in vivo indications target genetic liver diseases, including ATTR, AATD and PH-1, and infectious diseases such as HBV. Our initial efforts on in vivo delivery focus on the use of LNPs for delivery of the CRISPR/Cas9 complex to the liver.

Genetic diseases:

Transthyretin Amyloidosis Program (Knockout Strategy)

Transthyretin (TTR) is a protein produced primarily in the liver, encoded by the TTR gene. This protein carries retinol (vitamin A) and thyroxine (thyroid hormone) throughout the body. Certain mutations can cause the protein to aggregate and accumulate in tissues, resulting in a disorder called TTR-mediated amyloidosis (ATTR). Over 120 different genetic mutations are currently known to cause ATTR. Protein accumulation in peripheral nerves or the heart can result in a severe loss of nerve or cardiac function. Mutations leading to nerve disease cause a syndrome called familial amyloidotic polyneuropathy (FAP), whereas those leading to heart disease cause a syndrome called familial amyloidotic cardiomyopathy (FAC). Ongoing amyloid deposition in tissues due to disease progression results in the development of cardiomyopathy and other cardiac symptoms observed in FAC patients. Typical onset of disease symptoms occurs during adulthood and can be fatal within two to 15 years. Estimates suggest that approximately 50,000 patients suffer from ATTR worldwide.

We believe that we can apply CRISPR/Cas9 technology to potentially cure ATTR by knocking out expression of the TTR gene in the liver. We expect this approach to greatly reduce or eliminate the production of the TTR protein, which should slow or stop the accumulation of protein in the nerves and the heart. Current treatments and ongoing clinical trials in FAP have shown a significant correlation between TTR protein reduction and clinical benefit. Additionally, these studies suggest that loss of TTR gene expression from the liver would be well-tolerated in adult humans. Accordingly, we believe targeting TTR genes with CRISPR/Cas9 may improve patient outcomes by potentially eliminating defective TTR protein in a single or small number of treatments, as opposed to life-long therapy. We have assessed delivery of guide RNAs directed at the TTR gene via LNPs and have achieved high levels of liver cell editing in vitro and in vivo as well as reduction of serum TTR protein in multiple species. In mice, with a single dose of LNP, we achieved and maintained an approximately 97 percent reduction in serum TTR protein levels

through 12 months. This TTR reduction was accomplished by approximately 70 percent sustained editing at the target DNA site in the liver. In rats, we have observed up to 91 percent reduction in serum TTR protein levels and up to 66 percent editing at the target DNA site in the subject animals.

In preliminary NHP studies currently at varying points of progress, we achieved liver genome editing rates using CRISPR/Cas9 delivered via our proprietary LNP system ranging from 0.10 percent up to 32.0 percent after a single

dose with various exploratory gRNA, LNP formulations and dosing regimens. In NHPs redosed with a subsequent application of our LNP formulations, which were well tolerated, we observed further editing surpassing the levels achieved after a single dose. We continue to improve upon our current LNP formulations, and expect to begin IND-enabling activities for a human therapeutic as soon as mid-2018.

Clinical Development Pathway

Our first in-human studies in ATTR are expected to take place in patients with ATTR who have started to exhibit symptoms related to amyloid deposition. The key objective of these studies will be to show that the therapy can be delivered safely to the patient. A secondary objective will be to identify early indicators of efficacy, which may include reductions in serum levels of TTR protein. We expect that the results of our preclinical studies, and discussions with the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and other relevant regulatory agencies as well as patient advocacy groups will be important in informing our trial design. Under our collaboration agreement, we expect to co-develop therapies targeting ATTR with Regeneron.

Alpha-1 Antitrypsin Deficiency Program (Knockout, Repair, and Insertion Strategies)

AATD is an inherited genetic disorder that may cause lung or liver disease. The lung disease may result in chronic obstructive pulmonary disease (COPD), a progressive disease that causes substantial morbidity and mortality while the liver disease is characterized by inflammation and cirrhosis of the liver. In the United States, an estimated 60,000 to 100,000 people have AATD, which is the result of a mutation in the SERPINA1 gene that normally produces secreted alpha-1 antitrypsin (AAT) protein. AAT is a protease inhibitor that blocks the activity of various enzymes such as neutrophil elastase, which is an enzyme that fights infections, but when not adequately controlled by AAT, can attack normal tissues, such as lung tissue.

The most common form of AATD arises when a patient has a mutation in both copies of the SERPINA1 gene, which causes AAT to aggregate inside liver hepatocytes, rather than being secreted from the liver. The inability to secrete AAT leaves the lung unprotected from neutrophil elastase and can result in pulmonary disease. The pulmonary consequences of AATD can sometimes culminate in COPD. Estimates suggest that between 1% and 2% of all cases of COPD in the United States have AATD as the underlying cause. In some forms of the disease, AAT accumulates in the liver, causing liver inflammation and cirrhosis, which leads to liver damage, scarring and in the most severe cases, liver failure or cancer. Liver disease associated with AATD is diagnosed from infancy to adulthood, whereas lung disease is most common in adult patients.

We believe that we can apply the CRISPR/Cas9 technology to cure AATD by addressing the defective SERPINA1 gene. We are evaluating multiple editing approaches—knockout, insertion and repair. Our knockout program for AATD will be best suited for patients with AATD-associated liver disease, as there is currently no effective way to reduce the accumulation of mutated AAT in the liver. With this strategy, we intend to eliminate production of the aberrant form of AAT by knocking out the mutated SERPINA1 gene with a Cas9-mediated cut. We believe this knockout will halt the production and accumulation of AAT in the liver but will not by itself address the lack of AAT circulation that leads to lung disease. Therefore, in this approach, we expect that patients with AATD-associated lung disease may have to be treated with other therapies, such as plasma protein supplementation, to achieve levels of the normal form of AAT to be active against the lung disease.

We believe our insertion and repair approaches for AATD will address the lung disease as well as the liver disease. With either of these strategies, we intend to either insert a normal copy of the SERPINA1 gene or correct the mutated SERPINA1 gene, which we believe will eliminate production of the aberrant form of AAT and also establish production of the normal protein in the liver. We believe both approaches could reduce or eliminate liver inflammation and increase levels of normal circulating AAT, which should protect the lung from neutrophil elastase,

thereby reducing or eliminating the need for other therapies, such as plasma protein augmentation therapy. There is preclinical evidence that hepatocytes with normal AAT may possess a growth advantage over those that express the mutated form, suggesting that correction of only a limited number of hepatocytes might be sufficient to address this disease. We expect the progress of these strategies to follow our AATD knockout program. Depending on the results of our studies and potential development requirements and timelines, we may decide to pursue one or more of these programs in clinical development.

Clinical Development Pathway

Our first-in-human studies are expected to take place in patients with AATD. The key objective of these studies will be to show that the therapy can be delivered safely to the patient. A secondary objective will be to identify early indicators of efficacy, which may include reductions in levels of mutated AAT protein, increases in production of normal circulating AAT protein and the required tests for determining liver and lung function. We will also seek to observe whether we have achieved pre-determined levels of properly functioning AAT in the blood, which has been used historically as a biomarker for approval of augmentation therapy approaches. We expect that the results of our preclinical studies and discussions with the FDA, EMA and other relevant regulatory agencies as well as the AATD community will be important for selecting the appropriate patients and endpoints for our clinical trials.

Inborn Errors of Metabolism (IEM) Program (Knockout, Repair and Insertion Strategies)

IEMs span a range of conditions, many severe or fatal, and frequently untreatable. Current treatment options for many IEMs are unsatisfactory and often include bone marrow or liver transplants, which pose the challenge of serious side effects including high risk of mortality in some cases. Individual IEMs are rare disorders, many having an incidence of fewer than 1 in 100,000 births. These diseases typically involve defects in single genes that code for enzymes that facilitate the metabolism of certain cellular components. Mutations in these enzymes can result in accumulation of metabolic intermediates, which are molecules that are precursor compounds in the chemical pathway leading to final metabolic products, that are toxic or interfere with normal biology. We have selected our lead IEM program, primary hyperoxaluria type 1 (PH-1), and are evaluating a large set of additional candidate IEMs, including argininosuccinic lyase deficiency; ornithine transcarbamylase deficiency; phenylketonuria (PKU) and maple syrup urine disease. Our selection criteria for our additional IEM indications include identifying diseases that originate in the liver, have well-defined mutations that can be addressed by a single knockout, repair or insertion approach, have readily measurable therapeutic endpoints with observable clinical responses, and for which there are no effective treatments.

Infectious Diseases

Hepatitis B Virus Program (Knockout Strategy)

Hepatitis B is an infection of the liver caused by HBV that can progress from acute to chronic infection in approximately 5-10% of infected adults. Chronic HBV can result in long-term health problems, including liver damage, liver failure, liver cancer or even death. Chronic HBV affects approximately 240 million people globally and contributes to an estimated 786,000 deaths each year. In the United States, an estimated 700,000 to 1.4 million persons have chronic HBV, with 2,000 to 4,000 HBV-related deaths per year.

We believe that treatment of HBV with a CRISPR/Cas9-based therapeutic has the potential to cure the disease as it could eradicate cccDNA reservoirs with one or a few treatment courses, potentially as a single agent or in combination with other therapies. For this therapeutic program, we intend to use a knockout strategy to destroy or render inactive the copies of HBV cccDNA in infected human cells. We believe this therapy could offer a significant improvement over existing treatment options that are life-long and do not cure the disease. We also believe it is possible that a common treatment solution can be developed for many or all genotypes of HBV through targeting portions of the cccDNA sequences that are the same across genotypes. In addition, there is potential to reduce viral resistance as the virus itself is eradicated.

According to published research studies, CRISPR/Cas9-mediated cuts can significantly reduce intracellular levels of cccDNA when tested in vitro. We believe we can use the CRISPR/Cas9 system to help eliminate the reservoirs of cccDNA in infected HBV patients. We are evaluating different knockout approaches to eliminate cccDNA in vivo, including cleaving the cccDNA in various individual or a combination of locations.

We have screened all of the potential guides from a specific HBV genomic sequence for their ability to cut HBV DNA, and also completed a bioinformatic analysis of potential CRISPR/Cas9 target sites in the HBV genome to identify guides that can be effective across HBV genotypes. In addition, we have conducted in vitro studies to assess the cccDNA reduction activity of these transiently delivered guides, as well as their ability to reduce viral antigen production. We continue to explore animal systems to assess the ability of our guide RNAs to reduce the levels of HBV virus and antigens in an in vivo setting.

Clinical Development Pathway

We expect our clinical development path to indicate evidence of safety and antiviral activity in patients infected with HBV, as a single agent or in combination with other therapies. The key study objective will be to show that the therapy can be delivered safely to the patient, with a secondary objective of identifying early indicators of antiviral effect. We expect that the results of our preclinical studies and discussions with the FDA, EMA and other relevant regulatory agencies, as well as with the HBV community, will be important for selecting the appropriate patients and endpoints for any future clinical trial.

Ex Vivo Pipeline

Through eXtellia, we are independently researching and developing proprietary engineered cell therapies to treat ex vivo various oncological and autoimmune diseases, for example using TCR-engineered T cells for immuno-oncology applications, engineered Tregs for autoimmune disorders and other cell types such as engineered induced pluripotent stem cells. Our approach to these products includes multiple avenues. In particular:

- We seek to develop allogeneic cellular therapies, which are cells derived from unmatched donors and modified outside of the human body to allow them to be administered to an unrelated patient. This effort is supported through our relationship with certain researchers at the Karolinska Institutet.
- Outside our Novartis collaboration, we are exploring non-CAR-T cellular approaches that utilize immune cells, including TCR based therapy, to target immuno-oncology indications. For example, in our existing collaboration with Ospedale San Raffaele, we are identifying optimized TCR sequences of an antigen target that could be used to treat certain cancers.
- We are also exploring methods to apply CRISPR/Cas9 editing to CD4 cells to induce non-reverting regulatory T cell phenotype for therapies that address auto-immune disease.

Our partnered ex vivo programs are in CAR-T cell and HSC applications. Under our strategic collaboration with Novartis, our CAR-T cell program is exclusive to Novartis. We retain the right to develop and commercialize certain of the HSC programs that we discover with Novartis while others will be proprietary to Novartis.

For our ex vivo programs requiring delivery to extracted cells such as HSCs or T cells for modification, we initially plan to deliver the CRISPR/Cas9 complex by electroporation. In parallel with electroporation, we are exploring alternative technologies for delivery to cells ex vivo that may provide advantages in delivery efficiency or cell viability.

CAR-T Cell Program

In 2017, the first CAR-T cell products, including Novartis' Kymriah (CTL019), were approved by the FDA to treat certain oncology indications such as pediatric acute lymphoblastic leukemia (ALL) and Non-Hodgkins Lymphoma (NHL). Additional therapies are being developed for blood cancers such as acute myeloid leukemia (AML), multiple myeloma (MML) and chronic lymphocytic leukemia (CLL), as well as several other solid-rumor cancers. In CAR-T cell therapy, naturally-occurring immune cells, specifically T cells, are modified ex vivo by inserting a chimeric antigen receptor (CAR) into the T cells, thereby activating an immune response against cancer cells.

CAR-T cell products can benefit from the application of CRISPR/Cas9 in multiple ways.

- CRISPR/Cas9 could be used to create a universal donor CAR-T cell by knocking out cell surface markers that cause a patient's immune system to recognize another person's cells as foreign. Allowing multiple patients to be treated using cells from a single donor could significantly streamline manufacturing and make CAR-T cell therapy more widely accessible.

- CRISPR/Cas9 could be used to modify the T cells to enhance their survival or activity against cancer cells.

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- CRISPR/Cas9 could be used to introduce the CAR into a precise location in the genome with a specific integrated copy number, as opposed to the current method involving semi-random integration, thus potentially improving the safety profile of the resulting cells.
- CRISPR/Cas9 could be used to knockout one or more of the proteins believed to be responsible for certain serious side effects that can result in dangerously high fevers or severe loss of blood pressure.

We could potentially combine two or more of these approaches to further enhance CAR-T cell therapy.

HSC Program

HSCs are the stem cells from which all of the various types of blood cells originate. HSCs can fully repopulate a patient's blood system following transplantation of bone marrow, mobilized peripheral blood or cord blood, which contain HSCs. There are multiple potential opportunities for treating patients using engineered HSCs, including to treat three common classes of blood-related disorders: such as hemoglobin disorders, including sickle cell disease and beta thalassemia; primary immune deficiencies, such as X-linked severe combined immunodeficiency, or X-SCID; and bone marrow failures, such as Fanconi anemia. There are limited treatment options available for these types of blood disorders, and available options typically require chronic blood transfusions or bone marrow transplants. These procedures are associated with significant risk, including mortality. We believe the CRISPR/Cas9 system can be used to potentially provide curative benefits by correcting the underlying genetic defect in blood cells of patients with these disorders. In additional applications, normal HSCs may be engineered ex vivo using CRISPR/Cas9 to express a therapeutic protein, which is then administered to patients in need of that protein.

Challenges of developing stem cell products can include the relatively low quantity of available cells for treatment and a limited ability to expand HSCs ex vivo. We expect to counter these challenges, if necessary, by employing a proprietary small molecule for HSC expansion to which Novartis has granted us rights. This small molecule could allow us to generate larger numbers of HSCs for re-implantation in patients after editing. We expect that the application of this technology will improve the performance of the blood cell graft and improve patient outcomes and recovery times as more therapeutic cells can be administered.

We are pursuing a number of potential gene targets and therapeutic indications in collaboration with Novartis. Under our collaboration with Novartis, we and Novartis each have the right to designate a fixed number of HSC therapeutic targets during multiple selection windows, with Novartis having the right of first target selections. Our selection criteria for development programs include, among others, disease severity, existing treatment options, delivery efficiency, the nature of the genetic edit required and the expected performance of cells modified by the procedure.

CAR-T Cell and HSC Development Collaboration with Novartis

Under this collaboration, we received an upfront technology access payment from Novartis of $10.0 million and are entitled to up to an additional $40.0 million, in the aggregate, in additional technology access fees and research payments during the five-year collaboration term, subject to certain credits and adjustments in favor of Novartis. In addition, we are eligible to earn up to $230.3 million in development, regulatory and sales-based milestone payments and mid-single-digit royalties, in each case, on a per-product basis for the products developed by Novartis, subject to certain target-based limitations. For more information regarding our ongoing collaboration with Novartis, see the section below entitled "Collaborations—Novartis Institutes for BioMedical Research, Inc."

Collaborations

To accelerate the development and commercialization of CRISPR/Cas9-based products in multiple therapeutic areas, we have formed, and intend to seek other opportunities to form, strategic alliances with collaborators who can augment our leadership in CRISPR/Cas9 therapeutic development.

Novartis Institutes for BioMedical Research, Inc.

In December 2014, we entered into a strategic collaboration agreement with Novartis, primarily focused on the development of new ex vivo CRISPR/Cas9-based therapies using CAR-T cells and HSCs.

Under the terms of the collaboration, we and Novartis may research potential therapeutic, prophylactic and palliative ex vivo applications of our CRISPR/Cas9 technology in HSCs and CAR-T cells. We and Novartis agreed to conduct research of HSC targets under a research plan agreed upon by both parties. Within the HSC therapeutic space, Novartis may obtain exclusive rights to a limited number of these HSC targets, to be selected by Novartis in a series of selection windows. We have the right to choose a limited number of HSC targets for our exclusive development and commercialization per the specified selection schedule. Following these selections by Novartis and us, Novartis may obtain rights to research an additional limited number of HSC targets on a non-exclusive basis. Novartis is required to use commercially reasonable efforts to research, develop, and commercialize a specified number of HSC products directed to each of their selected HSC targets.

We have also agreed to collaborate with Novartis on research activities for CAR-T cell targets pursuant to the CAR-T cell program research plan approved by the CAR-T cell subcommittee of the collaboration's joint steering committee. After completion of the activities contemplated by the CAR-T cell program research plan, Novartis will assume sole responsibility for developing any products arising from that research plan and the costs and expenses of developing, manufacturing and commercializing its selected research targets. Novartis is required to use commercially reasonable efforts to research, develop or commercialize at least one CAR-T cell product directed to each of its selected CAR-T cell targets.

Starting in December 2017 and through the end of the collaboration, Novartis has the option to select a limited number of targets for research, development and commercialization of in vivo therapies using our CRISPR/Cas9 platform, on a non-exclusive basis. Following Novartis' selection of each in vivo target, Novartis may offer us the right to participate in the research and development of such targets, in which case an in vivo program research plan for such target will be entered into between us and Novartis. Novartis is required to use commercially reasonable efforts to research, develop and commercialize at least one in vivo product directed to each of its selected in vivo targets. Novartis' in vivo target selections are subject to certain restrictions, including that the targets, or all targets within a limited number of organs: (i) have not already been reserved by us pursuant to our limited right to do so under the agreement; (ii) are not the subject of a collaboration or pending collaboration with a third party; and (iii) are not the subject of ongoing or planned research and development by us.

Under the agreement, we received an upfront technology access payment of $10.0 million and are entitled to additional technology access fees of $20.0 million and quarterly research payments of $1.0 million, or up to $20.0 million in the aggregate, during the five-year research term. In addition, for each product under the collaboration, subject to certain conditions, we may be eligible to receive (i) up to $30.3 million in development milestones, including for the filing of an investigational new drug application and for the dosing of the first patient in each of Phase IIa, Phase IIb and Phase III clinical trials, (ii) up to $50.0 million in regulatory milestones for the product's first indication, including regulatory approvals in the United States, (U.S.), and the European Union (EU), (iii) up to $50.0 million in regulatory milestones for the product's second indication, if any, including U.S. and EU regulatory approvals, (iv) royalties on net sales in the mid-single digits, and (v) net sales milestone payments of up to $100.0 million. We may also be eligible to receive payments for: (i) each additional HSC target selected by Novartis beyond its initial defined allocation, (ii) each in vivo target that Novartis selects and (iii) any exercise by Novartis of certain license options under the agreement. Additionally, at the inception of the arrangement, Novartis invested $9.0 million to purchase our Class A-1 and Class A-2 Preferred Units. The difference between the cash proceeds received from Novartis for the units and the $11.6 million estimated fair value of those units at the date of issuance was determined to be $2.6 million. Accordingly, $2.6 million of the upfront technology access payment was allocated to record the preferred units purchased by Novartis at fair value.

We granted to Novartis a license to our CRISPR/Cas9 platform technology and Novartis granted us a non-exclusive license to its small molecule for HSC expansion and to its LNP platform technology to research, develop and commercialize HSC and in vivo products, respectively. Our license grant to Novartis of our CRISPR/Cas9 platform

technology, including a sublicense to certain platform rights licensed from Caribou Biosciences, Inc. ("Caribou"), is exclusive in the HSC, CAR-T cell and in vivo fields with respect to each target selected by Novartis pursuant to the agreement and the research plan as long as Novartis continues to use commercially reasonable efforts to research, develop, and commercialize products directed to such targets. Upon the expiration of the collaboration term, Novartis shall have the option to access and obtain a non-exclusive license to our CRISPR/Cas9 platform technology to research, develop and commercialize potential therapeutic, prophylactic and palliative products and services for a limited number of certain approved targets selected by Novartis, exercisable upon written notice to us

within a specified time after the expiration of the collaboration term. Such approved targets are subject to certain restrictions, including that the targets may not have been already reserved by us pursuant to our limited right to do so under the agreement, may not be the subject of an existing out license of our CRISPR/Cas9 platform to a third party and may not be the subject of ongoing or planned research and development by us. This non-exclusive license will have a term of five years commencing upon the completion of the technology transfer by us enabling Novartis to practice such licensed rights, and Novartis may not select more than a specified number of approved targets in each year of this license term.

Intellectual property that we develop within the collaboration related to our CRISPR/Cas9 platform will be owned solely by us, while all other intellectual property developed within the collaboration, including intellectual property covering products arising from the collaboration, will be jointly owned by us and Novartis.

The collaboration term ends in December 2019. The term of the agreement expires on the later of (i) the expiration of Novartis' payment obligations under the agreement and (ii) the date of expiration of the last-to-expire of the patent rights licensed to us or Novartis under the agreement. Novartis' royalty payment obligations expire on a country-by-country and product-by-product basis upon the later of (i) the expiration of the last valid claim of the royalty-bearing patents covering such product in such country or (ii) 10 years after the first commercial sale of such product in such country. We may terminate the agreement if Novartis or its affiliates institute a patent challenge against our intellectual property rights, and all improvements thereto, licensed to Novartis under the agreement. Novartis may terminate the agreement, without cause, upon 90 days' written notice to us subject to certain conditions, including its payment of any accrued and future obligations as if the collaboration had continued through December 2019. Either party may terminate the agreement in the event of the other party's uncured material breach or bankruptcy—or insolvency-related events.

Regeneron Pharmaceuticals, Inc.

In April 2016, we entered into a license and collaboration agreement with Regeneron. The agreement includes a product component to research, develop and commercialize CRISPR/Cas-based therapeutic products primarily focused on gene editing in the liver as well as a technology collaboration component, pursuant to which we and Regeneron will engage in research and development activities aimed at discovering and developing novel technologies and improvements to CRISPR/Cas technology to enhance our gene editing platform. Under this agreement, we also may access the Regeneron Genetics Center and proprietary mouse models to be provided by Regeneron for a limited number of our liver programs.

Under the terms of our collaboration, we and Regeneron have agreed to a target selection process, whereby Regeneron may obtain exclusive rights for up to 10 targets to be chosen by Regeneron during the collaboration term, subject to various adjustments and limitations set forth in the agreement. Of these 10 total targets, Regeneron may select up to five non-liver targets, while the remaining targets must be focused in the liver.

At the inception of the agreement, Regeneron selected the first of its 10 targets, which will be subject to a co-development and co-commercialization arrangement between us and Regeneron. We retain the exclusive right to solely develop products for certain indications, including AATD and HBV. During the target selection process, we have the right to choose additional liver targets for our own development using commercially reasonable efforts. Certain targets that either we or Regeneron select may be subject to further co-development and co-commercialization arrangements at our or Regeneron's option, as applicable, which either can exercise pursuant to defined conditions. In addition, subject to certain restrictions, Regeneron will be able to replace a limited number of targets with substitute targets upon the payment of a specified replacement fee, in which case exclusive rights to the replaced target revert to us. Regeneron's target selections are subject to certain additional restrictions, including that non-liver targets are not the subject of ongoing or planned research and development by us or are not the subject of a collaboration or pending

collaboration with a third party.

Research activities under the collaboration will be governed by evaluation and research and development plans that will outline the parties' responsibilities under, anticipated timelines of and budgets for, the various programs. We will assist Regeneron with the preliminary evaluation of liver targets, and Regeneron will be responsible for preclinical research and the conduct of clinical development, manufacturing and commercialization of products directed to each of its exclusive targets under the oversight of a joint steering committee. We may assist, as

requested by Regeneron, with the later discovery and research of product candidates directed to any selected target. For each selected target, Regeneron is required to use commercially reasonable efforts to submit regulatory filings necessary to achieve initial IND acceptance for at least one product directed to each applicable target, and following IND acceptance for at least one product, to develop and commercialize such product.

In connection with this collaboration, Regeneron agreed to purchase $50.0 million of our common stock in a private placement concurrent with our initial public offering, and we received a nonrefundable upfront payment of $75.0 million. In addition, we are eligible to earn, on a per-licensed target basis, up to $25.0 million, $110.0 million and $185.0 million in development, regulatory and sales-based milestone payments, respectively. We are also eligible to earn royalties ranging from the high single digits to low teens, in each case, on a per-product basis, which royalties are potentially subject to various reductions and offsets and are further subject to our existing up to mid-single-digit royalty obligations under a license agreement with Caribou. In addition, Regeneron is obligated to fund 50.0% of certain research and development costs for the ATTR program, the first target selected by Regeneron, which will be subject to a co-development and co-commercialization arrangement between us and Regeneron.

We have granted Regeneron exclusive rights to develop and commercialize products directed to its selected targets. The parties will jointly own intellectual property created as part of the technology collaboration and target-specific research plans, subject to certain exceptions where Regeneron will solely own certain intellectual property specific to its products and we will solely own certain CRISPR/Cas intellectual property arising during target evaluation activities. Each party has granted the other party specified intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the agreement.

The collaboration term ends in April 2022, provided that Regeneron may make a one-time payment of $25.0 million to extend the term for an additional two-year period. The agreement will continue until the date when no royalty or other payment obligations are due, unless earlier terminated in accordance with the terms of the agreement. Regeneron’s royalty payment obligations expire on a country-by-country and product-by-product basis upon the later of (i) the expiration of the last valid claim of the royalty-bearing patents covering such product in such country, (ii) 12 years from the first commercial sale of such product in such country, or (iii) the expiration of regulatory exclusivity for such product. We may terminate the agreement on a target-by-target basis if Regeneron or any of its affiliates institutes a patent challenge against our CRISPR/Cas or certain other background patent rights. We may also terminate the agreement on a target-by-target basis if Regeneron does not proceed with the development of a product directed to a selected target within specified periods of time. Regeneron may terminate the agreement, without cause, upon 180 days written notice to us, either in its entirety or on a target-by-target basis, in which event, certain rights in the terminated targets and associated intellectual property revert to us, as described in the agreement. Following such termination, we will owe Regeneron royalties in the low to mid-single digits on any terminated targets that we subsequently commercialize on a product-by-product basis for a period of 12 years after the first commercial sale of any such products. Either party may terminate the agreement either in its entirety or with respect to the technology collaboration or one or more of the targets selected by Regeneron, in the event of the other party’s uncured material breach.

Potential Future Collaborations

We view strategic partnerships as important drivers for helping accelerate our goal of rapidly treating patients. The potential application of CRISPR/Cas9 is extremely broad, and we plan to continue to identify partners who can contribute meaningful resources and insights to our programs and allow us to more rapidly bring scientific innovation to a broader patient population.

Intellectual Property

We believe we are well positioned in terms of our intellectual property because we:

- have built, and intend to expand, a broad worldwide portfolio of intellectual property, including patents and patent applications, in areas relevant to the development and commercialization of human therapeutic products using CRISPR/Cas9 technology;
- protect our intellectual property by maintaining trade secrets relating to our proprietary technology innovations and know-how; and
- intend to take additional steps, where appropriate, to further protect our intellectual property rights, including, for example, through the use of copyright protection and regulatory protection available via orphan drug designations, data exclusivity, market exclusivity, and patent term extensions.

Our licensed patent portfolio encompasses foundational filings on the use of CRISPR/Cas9 systems for gene editing, improvement modifications of these CRISPR systems, LNP technologies for delivering protein/nucleic acid complexes and RNA into cells, and cell expansion technology relevant to stem cell-based therapies. We access these patent estates through licenses from Caribou and Novartis. We also actively apply for, maintain, and plan to defend and enforce, as needed, our internally developed and externally licensed patent rights. Furthermore, we continue to search for and evaluate opportunities to in-license intellectual property relevant to our targeted therapeutic programs and platforms and to develop and acquire new intellectual property in collaboration with third parties.

Our portfolio of patent rights includes the following:

Caribou Biosciences In-Licensed Intellectual Property

In July 2014, we entered into a license agreement with Caribou, as subsequently amended and supplemented, for an exclusive, worldwide license for human therapeutic, prophylactic, and palliative uses, except for anti-fungal and anti-microbial uses, defined in the license agreement as our field of use, of any CRISPR/Cas9-related patents and applications owned, controlled or licensed by Caribou as well as companion diagnostics to our product or product candidates. The license agreement also included exclusive rights in our field of use to any CRISPR/Cas9-related intellectual property developed by Caribou after July 16, 2014 and through a cut-off date of January 30, 2018. The agreement further includes a non-exclusive research license to conduct research and development on product candidates and products. The Caribou licensed patent portfolio includes several U.S. and foreign patents and patent applications owned by Caribou, and U.S. and foreign patents and patent applications co-owned by The Regents of the University of California, the University of Vienna and Dr. Emmanuelle Charpentier, as well as U.S. and foreign patents and patent applications owned or controlled by Pioneer Hi-Bred and its affiliates. We have the right to grant sublicenses to the Caribou licensed patent portfolio to third parties in our field of use. Caribou retains the right to practice the licensed intellectual property in all other fields, including for its own specific therapeutics purposes, provided it does not pertain to the application of CRISPR/Cas9 technology to the development of products in our field of use.

Pursuant to a services agreement entered into with Caribou in parallel with the license agreement, we also received two years of research and development services from Caribou, which ended in November 2016. Any intellectual property developed under the services agreement is owned by Caribou and is included in, and subject to the terms of, our license agreement with Caribou.

In relation to our founding, we issued Caribou 8,110,599 shares of our junior preferred stock. We paid Caribou $5.0 million over the term of the two-year services agreement; and have agreed to pay 30.0% of Caribou’s patent prosecution, filing, and maintenance costs for the intellectual property included in the license agreement amounting to a total of $2.6 million paid through December 31, 2017. We also granted Caribou an exclusive, royalty-free,

worldwide license, with the right to sublicense, to any CRISPR/Cas9 patents, patent applications and know-how in Caribou's retained fields of use owned or developed by us between July 16, 2014 and a cut-off date of January 30, 2018. Caribou, which is obligated to pay a portion of our patent filing, prosecution and maintenance costs for any such licensed intellectual property, also has an option to sublicense any CRISPR/Cas9 intellectual property in-licensed by us for uses and activities in its retained field of use.

The Caribou license agreement grants us sublicenses in our field of use to intellectual property in-licensed by Caribou from The Regents of the University of California and the University of Vienna. Further, under the license agreement, we had an option to sublicense for our field of use any new intellectual property in-licensed by Caribou through January 30, 2018. In July 2015, we exercised our option to sublicense a portfolio in-licensed by Caribou from Pioneer Hi-Bred International, according to the terms described below.

The term of the Caribou license is until the expiration of the last-to-expire patent right that is licensed to either party. We must use commercially reasonable and diligent efforts to research, develop, manufacture and commercialize at least one product. Either party may terminate the agreement in the event of the other party's uncured material breach, bankruptcy or insolvency-related events, or breach of its obligations with respect to the included in-licenses. The license agreement with Caribou also gives us access, in our field of use, to Caribou internally developed IP. Since March 2013, Caribou has filed over 50 patent applications in the United States and internationally, which relate to the CRISPR/Cas platform, including modified and improved CRISPR/Cas9 systems or components, and methods of use that are part of our license. We cannot ensure that these applications will lead to issued claims that cover our products or activities. Any patents that grant from these applications will expire in or after 2034, assuming payment of necessary maintenance fees.

The Regents of the University of California and the University of Vienna Intellectual Property

The Regents of the University of California and the University of Vienna (collectively, UC/Vienna) co-own with Dr. Emmanuelle Charpentier a worldwide patent portfolio, which covers methods of use and compositions relating to engineered CRISPR/Cas9 systems for, among other things, cleaving or editing DNA and altering gene product expression in various organisms, including humans. We refer to this co-owned worldwide patent portfolio as the UC/Vienna/Charpentier patent family. The earliest claimed priority date for this patent family is May 25, 2012. As of December 31, 2017, this family includes granted patents in many jurisdictions outside the United States, including for example the United Kingdom, Germany, Australia, China and the approximately 40 countries that are members of the European Patent Convention. Corresponding applications are being prosecuted in the United States Patent and Trademark Office (USPTO) and other patent agencies across the world. Any patents that ultimately issue from this family and are appropriately maintained will expire in or after 2033.

Caribou entered into an exclusive, worldwide license in all fields, with the right to sublicense, for this patent family with UC/Vienna in April 2013 solely under UC/Vienna ownership rights. Caribou's license remains in effect for the life of the last-to-expire patent or last-to-be-abandoned patent application licensed, whichever is later. Through our license agreement with Caribou, we have an exclusive sublicense to UC/Vienna's interest in this foundational CRISPR/Cas9 patent family for use in human therapeutics, except for anti-fungal and anti-microbial uses as defined in the license agreement as our field of use. For products covered by this license and their companion diagnostics, we will owe mid-single-digit royalties on net sales. In addition, we may be subject to milestone payments of $0.1 million upon the first filing of an investigational new drug application, a total of $0.5 million for Phase II and Phase III clinical trials, $0.5 million to $1.0 million for each of the first three approved new drug applications or biologics license applications in the United States, and $0.2 million for each of the first three approved indications in Europe. Caribou has the right to terminate its agreement with UC/Vienna at any time or the agreement may be terminated due to an uncured material breach. We cannot guarantee that Caribou will maintain the UC/Vienna license for its full term. Should the license between Caribou and UC/Vienna be terminated for any reason, any compliant Caribou sublicenses as of the termination date will remain in effect and will be assigned to UC/Vienna in place of Caribou. Specifically, if we are in compliance with our obligations under our sublicense and Caribou and UC/Vienna terminate their agreement, UC/Vienna would replace Caribou as our licensor.

On April 13, 2015, UC/Vienna and Dr. Charpentier (collectively, UC/Vienna/Charpentier) jointly filed a request with the USPTO asking that an interference be declared between a UC/Vienna/Charpentier patent application and certain

patents issued to the Broad Institute, Massachusetts Institute of Technology and the President and Fellows of Harvard College (collectively, the Broad Institute patent family), which claim aspects of CRISPR/Cas9 systems and methods to edit genes in eukaryotic cells, including human cells. The Broad Institute patent family includes, for example, US 8,697,359, issued on April 15, 2014. The earliest claimed priority date for the Broad Institute patent family is December 12, 2012. On January 11, 2016, the Patent Trial and Appeal Board (PTAB) of the USPTO declared an interference involving one UC/Vienna/Charpentier application, 12 Broad issued patents and a Broad patent application. On February 15, 2017, the PTAB dismissed the proceeding finding that the respective patent claims involved in the interference were distinct such that they did not meet the legal requirement to proceed with

the interference. As a result of this proceeding's dismissal, the PTAB did not make a decision regarding which party actually first invented the use of CRISPR/Cas9 systems and methods to edit genes in eukaryotic cells. In April 2017, UC/Vienna/Charpentier appealed to the U.S. Court of Appeals for the Federal Circuit seeking a review and reversal of the PTAB's decision to terminate the interference, and briefing on the appeal was completed in November 2017. Unless otherwise resolved, the Federal Circuit is expected to render a decision after an oral hearing. In addition, UC/Vienna/Charpentier continue to prosecute other patent claims covering the CRISPR/Cas9 inventions, which could also result in allowable or issued patents in the United States. Certain of the claims being prosecuted by UC/Vienna/Charpentier, if found allowable by the USPTO, could lead to interference proceedings against patents or patent applications owned by other parties, including the Broad Institute patent family with respect to certain claims relating to the use of CRISPR/Cas9 in eukaryotic cells. We cannot be certain which of these results, if any, will actually occur or at what time, and the effects that any such results may have on us and our intellectual property position are currently unknown.

Pioneer Hi-Bred International (DuPont Company) Intellectual Property

Pioneer Hi-Bred and its affiliates, including the DuPont Company, have licensed to Caribou on a worldwide basis, various patent families relating to CRISPR/Cas systems, components and methods of use generally and CRISPR/Cas9 specifically in certain fields, which include Intellia's field of use under our license agreement with Caribou. In July 2015, we exercised our option under the license agreement with Caribou to sublicense these Pioneer patent families in our field of use. The license from Pioneer to Caribou will expire upon the expiration, abandonment or invalidation of the last patent or patent application licensed from Pioneer to Caribou.

The licensed Pioneer portfolio includes a family of applications filed by Vilnius University that discloses the components of a CRISPR/Cas9 system required for gene editing in non-bacterial organisms. On May 2, 2017, the USPTO issued U.S. Patent No. 9,637,739, with claims covering the in vitro assembly and use of a recombinant CRISPR/Cas9 complex to modify DNA. Patents obtained from this patent family will expire in or after 2033, assuming payment of necessary maintenance fees. We cannot ensure that these additional applications in this family will lead to issued claims that cover our products or activities.

Invention Management Agreement

On December 15, 2016, we entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement (the Invention Management Agreement), with The Regents of the University of California, University of Vienna, Dr. Charpentier, Caribou, CRISPR Therapeutics AG, ERS Genomics Ltd. and TRACR Hematology Ltd. Under the Invention Management Agreement, Dr. Charpentier retroactively consented to UC/Vienna's CRISPR/Cas9 license to Caribou as well as Caribou's sublicensing to Intellia certain of its rights to the UC/Vienna/Charpentier CRISPR/Cas9 intellectual property, subject to the restrictions of our license from Caribou. Under the agreement, the parties commit to maintain and coordinate the prosecution, defense and enforcement of the CRISPR/Cas9 foundational patent portfolio worldwide, and each of the co-owners of the intellectual property grants cross-consents to all existing and future licenses and sublicenses based on the rights of another co-owner. The Invention Management Agreement also includes retroactive approval by certain parties of certain prior assignments of interests in patent rights to other parties, and provides for, among other things, (i) good faith cooperation among the parties regarding patent maintenance, defense and prosecution, (ii) cost-sharing arrangements, and (iii) notice of and coordination in the event of third-party infringement of the subject patents. Unless earlier terminated by the parties, the Invention Management Agreement will continue in effect until the later of the last expiration date of the UC/Vienna/Charpentier patents underlying the CRISPR/Cas9 technology, or the date on which the last underlying patent application is abandoned.

Novartis In-Licensed Intellectual Property

Our December 2014 strategic collaboration and license agreement with Novartis grants us worldwide, non-exclusive, royalty-free rights to a portfolio of 14 Novartis patent families containing granted patents and pending applications in the United States and internationally relating to LNP compositions, methods of use and modified nucleic acids. The license permits us to use the Novartis LNPs to develop therapeutic, prophylactic, and palliative CRISPR-based in vivo products. The earliest claimed priority dates for the licensed patent families range from December 2009 through June 2013, and accordingly will expire by or after December 2030. The term of the license

continues until the expiration of the last-to-expire patent right that is licensed to either party. If we attempt to challenge any of the patents in the licensed families, Novartis may terminate the license on a patent-by-patent basis. We cannot guarantee that our products or delivery methods will be covered by issued claims in these families.

In addition, Novartis has also granted us rights to use its proprietary small molecule for HSC expansion. Our rights to this technology are subject to a single-digit royalty based on whether we develop and commercialize the relevant product solely or in collaboration with another third party.

Under our agreement with Novartis, any platform intellectual property developed as part of the collaboration is owned solely by us, while all other intellectual property developed within the collaboration, including product-based intellectual property, is jointly owned by us and Novartis. We cannot guarantee that intellectual property filed based on collaboration data will result in issued claims covering our products or delivery methods. Under our agreement with Novartis, we have also granted Novartis a sublicense to the intellectual property we license under our agreement with Caribou for the Novartis-selected HSC and CAR-T cells products, and in vivo products if applicable, with such sublicense being exclusive as long as Novartis uses commercially reasonable efforts to develop and commercialize those products.

Manufacturing

We currently have no commercial manufacturing or cell processing capabilities. We are exploring creating internal capabilities, as well as contracting qualified third-party organizations, to produce or process bulk compounds, formulated compounds, viral vectors or engineered cells for IND-supporting activities and early stage clinical trials. We expect that clinical and commercial quantities of any compound, vector, or engineered cells that we may seek to develop will be manufactured in facilities and by processes that comply with FDA and other regulations. At the appropriate time in the product development process, we will determine whether to establish our own manufacturing facilities or continue to rely on third parties to manufacture commercial quantities of any products that we may successfully develop.

Competition

The biotechnology industry is extremely competitive in the race to develop new products. While we believe we have significant competitive advantages with our industry-leading expertise in gene editing, clinical development expertise and dominant intellectual property position, we currently face and will continue to face competition for our development programs from companies that use genome editing or gene therapy development platforms and from companies focused on more traditional therapeutic modalities such as small molecules and antibodies. The competition is likely to come from multiple sources, including larger pharmaceutical companies, biotechnology companies and academia. Many of these competitors may have access to greater capital and resources than us. For any products that we may ultimately commercialize, not only will we compete with any existing therapies and those therapies currently in development, but we will also have to compete with new therapies that may become available in the future.

Competitors in our efforts to provide genetic therapies to patients can be grouped into at least three sets based on their product discovery platforms:

- genome editing companies focused on CRISPR/Cas9 including: Casebia Therapeutics, CRISPR Therapeutics, Inc., Editas Medicine, Inc., ToolGen, Inc. and Tracr Hematology Limited;
- other genome editing companies including: bluebird bio, Inc., Cellectis S.A., Homology Medicines, Inc., Poseida, Inc., Precision BioSciences, Inc., and Sangamo Therapeutics, Inc., and;
-

genome therapy companies developing in vivo or ex vivo therapies, such as cell therapies, including: bluebird bio, Inc., Cellectis S.A., Celgene Corporation (which acquired Juno Therapeutics, Inc.), Gilead Sciences, Inc. (which acquired Kite Pharma, Inc.), Novartis A.G. and Spark Therapeutics, Inc.

Our competitors will also include companies that are or will be developing other genome editing methods as well as small molecules, biologics, in vivo gene therapies, ex vivo cell therapies and nucleic acid-based therapies for the same indications that we are targeting with our CRISPR/Cas9-based therapeutics.

Government Regulation and Product Approval

We are subject to extensive regulation. We expect our future in vivo and ex vivo product candidates to be regulated as biologics. Biological products are subject to regulation under the Food, Drug and Cosmetic (FD&C) Act and the Public Health Service Act (PHS Act), and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving drug and biological products. Before clinical testing of biological products in the U.S. may begin, we must submit an IND to the FDA, which reviews the clinical protocol, and the IND must become effective before clinical trials may begin. We must also register our protocols with the National Institutes of Health (NIH) through its Recombinant DNA Advisory Committee (RAC) before initiating clinical testing and in some cases a public RAC review will be required.

Biologic products must be approved by the FDA before they may be legally marketed in the U.S. and by the appropriate foreign regulatory agencies before they may be legally marketed in foreign countries. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the Center for Biologics Evaluation and Research (CBER) regulates many biological products not regulated by the Center for Drug Evaluation and Research (CDER), including gene and cell therapies. Proposed human clinical trials involving nucleic acid transfer conducted at, or sponsored by, institutions receiving NIH funding for research with recombinant or synthetic nucleic acid molecules are also subject to review by the NIH RAC. Moreover, certain therapeutic protocols that raise important scientific, safety, medical, ethical, or social issues are discussed at the RAC's quarterly public meetings. While the FDA has not provided specific guidance on gene editing in humans, it has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy clinical trials for delayed adverse events, potency or other quality testing, and chemistry, manufacturing and control information in gene therapy INDs.

The FDA has provided guidance for the development of gene and cell therapy products that are relevant to the gene and cellular therapies we intend to develop. For example, the FDA has established the Office of Tissues and Advanced Therapies (OTAT) (previously known as Office of Cellular, Tissue and Gene Therapies) within CBER, to consolidate the review of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) to advise CBER on its reviews. In addition, the FDA has issued a growing body of clinical, chemistry, manufacturing and control (CMC) guidance and other guidance, all of which are intended to facilitate industry's development of these products. More recently and as part of the implementation of the 21st Century Cures Act, FDA has issued a number of draft guidances pertaining to Regenerative Medicine Advanced Therapies, that include cell therapies and, as interpreted by FDA, "gene therapies including genetically modified cells, that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy". A small number of gene therapy products have been approved by regulatory agencies. In 2012, the European Medicines Agency approved a gene therapy product called Glybera, which was the first gene therapy product approved by regulatory authorities anywhere in the Western world. And, in 2017, the FDA approved the first two cell-based gene therapy products

Ethical, social and legal concerns about gene-editing technology, gene therapy, genetic testing and genetic research could result in additional regulations restricting or prohibiting the processes we may use. Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any product candidates. New government requirements may be established that could delay or prevent regulatory

approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Drug and Biological Products Development Process

The FDA approves drugs through the New Drug Application (NDA) process and biologics through the Biologics License Application (BLA) process before they may be legally marketed in the U.S. This process generally involves the following:

- completion of extensive nonclinical, sometimes referred to as preclinical laboratory tests, and preclinical animal studies and applicable requirements for the humane use of laboratory animals and formulation studies in accordance with applicable regulations, including good laboratory practice (GLP);
- submission to the FDA of an IND application, which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practice (GCP) and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed product for its intended use;
- submission to the FDA of an NDA or BLA for marketing approval that includes substantial evidence of safety and efficacy or, for biological products, safety, purity, and potency, from nonclinical testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the product is produced to assess compliance with current good manufacturing practice (cGMP) 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 (cGTP) requirements for the use of human cellular and tissue products;
- positive results from potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the NDA or BLA; and
- FDA review and approval of the NDA or licensure of the BLA.

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

Where a study involving the transfer of nucleic acids into humans is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research or synthetic nucleic acid molecules, prior to the submission of an IND to the FDA, a protocol and related documentation is submitted to and the study is registered with the NIH Office of Biotechnology Activities (OBA), pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA; however, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee that reviews research proposals involving human-gene transfer research and discusses, if needed, protocols that raise novel or particularly important scientific, safety or ethical considerations. The RAC decides whether a protocol raises issues that warrant further discussion at its quarterly meetings, and the OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a particular protocol. RAC proceedings and reports are posted to the OBA web site and may be accessed by the public.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides

that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA may also impose clinical holds on a drug or biological product candidate at any time before or during clinical trials due to, among other reasons, safety concerns or non-compliance with regulatory requirements. If the FDA imposes a clinical hold, trials may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that result in the suspension or termination of such trials.

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

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

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

Post-approval clinical trials, sometimes referred to as Phase IV clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA typically advises 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.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the status of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other trials, tests in laboratory animals or in vitro testing that suggest a significant risk for human subjects, or any clinically important increase in the

rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening

suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase I, Phase II and Phase III clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor or its data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Sponsors of certain clinical trials of FDA-regulated products, including drugs and biologics, are required to register and disclose certain clinical trial information to NIH. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made publicly available as part of the registration at www.clinicaltrials.gov. Sponsors are also obligated to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved, up to a maximum of two years.

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

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

U.S. Review and Approval Processes

After the completion of clinical trials of a drug or biological product candidate, FDA approval of an NDA or BLA must be obtained before commercial marketing of the drug or biological product. The NDA or BLA must include results of product development, laboratory and animal trials, human trials, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act (PREA), an NDA, BLA or supplement to an NDA or BLA for a product candidate with certain novel characteristics must contain data to assess the safety and effectiveness of the product candidate for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The Food and Drug Administration Safety and Innovation Act (FDASIA) requires that a sponsor who is planning to submit a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of

administration submit an initial Pediatric Study Plan (PSP) within sixty days after an end-of-Phase 2 meeting or as may be agreed between the sponsor and FDA. The initial PSP must include, among other things, an outline of the pediatric study or studies that the sponsor plans to conduct, including, to the extent practicable, study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information, along with any other information specified in FDA regulations. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to

an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, or other clinical development programs. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug or biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the NDA or BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Under the Prescription Drug User Fee Act (PDUFA), as amended, each NDA or BLA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs or BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews an NDA or BLA to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any NDA or BLA that it deems incomplete or not properly reviewable at the time of submission, including for failure to pay required fees, and may request additional information. In this event, the application must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the NDA or BLA. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective (or, in the case of biological products, safe, pure and potent), and whether the product is being manufactured in accordance with cGMP, and in certain cases, cGTP, requirements to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the FDA review and approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary to assure the safe use of the drug or biological product candidate. If the FDA concludes a REMS is needed, the sponsor of the NDA or BLA must submit a proposed REMS; the FDA will not approve the application without a REMS, if required.

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

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

If a product receives regulatory approval, the approval may be significantly limited to specific diseases, dosages or patient subgroups or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings, precautions or adverse events be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA

may require post marketing clinical trials, sometimes referred to as Phase IV clinical trials, designed to further assess a product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under the PDUFA is to review 90% of BLAs in 10 months from the 60-day filing date, and 90% of priority BLAs in six months from the 60-day filing date, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs and its review goals are subject to change with PDUFA reauthorization. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Orphan Drug Designation

The FDA may grant Orphan Drug Designation to drugs or biological products intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the U.S., or, if it affects more than 200,000 individuals in the U.S., when there is no reasonable expectation that the cost of developing and marketing the drug or biological product for this type of disease or condition will be recovered from sales in the U.S. Orphan product designation must be requested before submission of an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

In the U.S., Orphan Drug Designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same orphan indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer with orphan exclusivity is unable to assure sufficient quantities of the approved orphan designated product. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity, which may permit off-label use for the orphan indication. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same drug or biological product as defined by the FDA for the same orphan indication or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drug and biological products that meet certain criteria. Specifically, new drug and biological products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request that the FDA designate the product as a Fast Track product at any time during the clinical development of the product, but ideally not later than the pre-NDA or pre-BLA meeting. The FDA may consider for review sections of the marketing application for a Fast Track product on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon

submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of that condition. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological

product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. Drug and biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a product subject to accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

In addition, under the provisions of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), the FDA established a Breakthrough Therapy Designation, which is intended to expedite the development and review of products that treat serious or life-threatening diseases or conditions. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the features of Fast Track designation, as well as more intensive FDA interaction and guidance. The Breakthrough Therapy Designation is a distinct status from both accelerated approval and priority review, but these can also be granted to the same product candidate if the relevant criteria are met. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.

Fast Track designation, priority review, accelerated approval and breakthrough therapy designation do not change the standards for approval but may expedite the development or approval process. Where applicable, we plan to request Fast Track and Breakthrough Therapy Designation for our product candidates. Even if we receive one or both of these designations for our product candidates, the FDA may later decide that our product candidates no longer meet the conditions for qualification. In addition, these designations may not provide us with a material commercial advantage.

Regenerative medicine advanced therapies (RMAT) designation

As part of the 21st Century Cures Act, the FD&C Act was amended to facilitate an efficient development program for, and expedite review of regenerative medicine advanced therapies, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA and for those granted accelerated approval post-approval requirements may be fulfilled through the submission of clinical evidence from clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior

to its approval.

Post-Approval Requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of drug and

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

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

Drug and biological product manufacturers and other entities involved in the manufacture and distribution of approved drugs and biological products are required to register their establishments with the FDA and certain other federal and state agencies, and are subject to periodic unannounced inspections by the FDA and certain other federal and state agencies for compliance with cGMP, and in certain cases, cGTP, requirements and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA or BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining

term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA or BLA plus the time between the submission date of an NDA or BLA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent within a 60-day period from the date the product is first approved for commercial marketing. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term

extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA or BLA. However, there can be no assurance that any such extension will be granted to us.

Under Hatch-Waxman Act, once an NDA is approved, potential competitors can rely upon the NDA upon expiration of certain patent and non-patent exclusivity periods, if any, to seek approval of competing products, including generic copies, via an abbreviated new drug application, or ANDA, or 505(b)(2) application. Both the ANDA and 505(b)(2) application processes allow a competitor to obtain approval without conducting all of the preclinical and clinical testing necessary for approval of a full NDA, which could result in a shorter and less expensive development and approval process.

The Hatch-Waxman Act provides for various periods of non-patent exclusivity to protect new drugs approved via a full NDA from premature competition. First, federal law provides a period of up to five years exclusivity following approval of a drug containing a new chemical entity, or NCE, defined as an active moiety that has not been approved previously. An active moiety, in turn, is defined as the molecule or ion responsible for the action of the drug substance. During this NCE exclusivity period, FDA cannot accept any ANDA or 505(b)(2) application referencing the NDA of the protected listed drug; however, the five-year exclusivity period is reduced to four years if the ANDA or 505(b)(2) application challenges to a listed patent for the protected drug product through submission of a paragraph IV certification (described below). Second, the Hatch-Waxman Act also provides for a period of three years of exclusivity following approval of a listed drug that contains a previously approved active ingredient if the FDA determines that new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are essential to the approval of the application. Three-year exclusivity is typically awarded for changes to an approved drug product, such as new indications, dosage forms or dosing regimens, and prohibits FDA from approving an ANDA or 505(b)(2) application with the protected innovation. As a general matter, three-year exclusivity does not prohibit the FDA from approving ANDAs or 505(b)(2) applications for competitive versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Additionally, in the event that the sponsor of the listed drug has properly informed the FDA of patents covering its listed drug, applicants submitting an ANDA or 505(b)(2) application referencing the listed drug are required to make one of four patent certifications for each listed patent, except for patents covering methods of use for which the ANDA or 505(b)(2) applicant is not seeking approval. If an applicant certifies its belief that one or more listed patents are invalid, unenforceable, or not infringed (and thereby indicates it is seeking approval prior to patent expiration), which is known as a paragraph IV certification, it is required to provide notice of its filing to the NDA sponsor and the patent holder within certain time limits. If the patent holder then initiates a suit for patent infringement against the ANDA or 505(b)(2) applicant within 45 days of receipt of the notice, the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until either 30 months have passed or there has been a court decision or settlement order holding or stating that the drug for which approval is being sought will not infringe the patents in question or that the patents are invalid or unenforceable. If the patent holder does not initiate a suit for patent infringement within the 45 days, the ANDA or 505(b)(2) application may be approved immediately upon successful completion of FDA review, unless blocked by another listed patent or regulatory exclusivity period. If the ANDA or 505(b)(2) applicant certifies that it does not intend to market its generic product before some or all listed patents on the listed drug expire (known as a Paragraph III certification), then the FDA cannot grant effective approval of the ANDA or 505(b)(2) application until those patents expire. The first of the ANDA applicants submitting substantially complete applications certifying that one or more listed patents for a particular product are invalid, unenforceable, or not infringed may qualify for an exclusivity period of 180 days running from when the generic product is first marketed, during which

subsequently submitted ANDAs containing similar certifications cannot be granted effective approval. The 180-day generic exclusivity can be forfeited in various ways, including if the first applicant does not market its product within specified statutory timelines. If more than one applicant files a substantially complete ANDA on the same day, each such first applicant will be entitled to share the 180-day exclusivity period, but there will only be one such period, beginning on the date of first marketing by any of the first applicants.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the Affordable Care Act), signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Starting in 2015, the FDA commenced licensing biosimilars under the BPCIA, and there are currently numerous biosimilars approved in the U.S. and Europe. The FDA has issued several draft and final guidance documents outlining an approach to review and approval of biosimilars and interchangeable biological products.

The BPCIA also contains various provisions regarding exclusivity for reference and interchangeable products and procedures for sharing and litigating patents covering the reference product. The BPCIA, however, is complex and only beginning to be interpreted and implemented by the FDA. In addition, proposed legislation has sought to reduce the 12-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation, and meaning of the BPCIA is subject to significant uncertainty.

Additional Regulation

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

Other Healthcare Laws

In addition to FDA restrictions on marketing of pharmaceutical and biological products, other U.S. federal and state healthcare regulatory laws restrict business practices in the pharmaceutical industry, which include, but are not limited to, state and federal anti-kickback, false claims, data privacy and security, and physician payment transparency laws.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting, receiving or providing any remuneration, directly or indirectly, overtly or covertly, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any item or service reimbursable, in whole or in part, under Medicare, Medicaid or other federal healthcare programs. The term “remuneration” has been broadly interpreted to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not meet the requirements of a statutory or regulatory exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute’s intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated. Penalties for violations of

the Anti-Kickback Statute include fines of up to $25,000 per violation and felony conviction punishable by imprisonment up to five years as well as possible exclusion from participation in federal healthcare programs, such as Medicare and Medicaid.

We may also be subject to data privacy and security regulation by both the federal government and the states and other jurisdictions outside the U.S. in which we conduct our business. HIPAA, as amended by the Health

Information Technology for Economic and Clinical Health Act (HITECH) and their respective implementing regulations, including the Final HIPAA Omnibus Rule published on January 25, 2013, impose specified requirements relating to the privacy, security and transmission of individually identifiable health information held by covered entities and their business associates. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating compliance efforts.

If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and individual imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

To the extent that any of our product candidates, once approved, are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or other transfers of value to healthcare professionals.

U.S. Foreign Corrupt Practices Act

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

Government Regulation Outside of the United States

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

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical or biological product for which we obtain regulatory approval. In the U.S. 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 our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Sales of any products for which we receive regulatory approval for commercial sale will therefore depend, in part, on the availability of coverage and adequate reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations.

The process for determining whether a third-party payor will provide coverage for a pharmaceutical or biological product typically is separate from the process for setting the price of such product or for establishing the reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a third-party payor not to cover our product

candidates could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Moreover, a third-party payor's decision to provide coverage for a pharmaceutical or biological product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. Additionally, coverage and reimbursement for new products can differ significantly from payor to payor. One third-party payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor separately and will be a time-consuming process.

The containment of healthcare costs has become a priority of federal, state and foreign governments as well as private third-party payors, and the prices of pharmaceutical or biological products have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost-effectiveness of pharmaceutical products, biological products, medical devices and medical services, in addition to questioning safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after FDA approval or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit.

Employees

As of February 28, 2018, we had 195 full-time employees, 152 of whom were primarily engaged in research and development activities and 68 of whom have an M.D. or Ph.D. degree.

Our Corporate Information

We were incorporated under the laws of the state of Delaware in May 2014 under the name AZRN, Inc. Our principal executive offices are located at 40 Erie Street Suite 130, Cambridge, Massachusetts 02139. Our telephone number is (857) 285-6200, and our website is located at www.intelliatx.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Annual Report on Form 10-K.

Available Information

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, are available free of charge on our website located at www.intelliatx.com as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission (the "SEC"). These reports are also available at the SEC's Internet website at www.sec.gov. The public may also read and copy any materials filed with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Washington D.C. 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-SEC-0330.

A copy of our Corporate Governance Guidelines, Code of Conduct and Business Ethics and the charters of the Audit Committee, Compensation Committee and Nominating and Corporate Governance Committee are posted on our website, www.intelliatx.com, under "Investor Relations".

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K for the year ended December 31, 2017 and in other documents that we file with the SEC, in evaluating the Company and our business. If any of the following risks and uncertainties actually occurs, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks described below are not intended to be exhaustive and are not the only risks facing the Company. New risk factors can emerge from time to time, and it

is not possible to predict the impact that any factor or combination of factors may have on our business, prospects, financial condition and results of operations.

Risks Related to Our Business, Technology and Industry

CRISPR/Cas9 genome editing technology is not yet clinically validated for human therapeutic use. The approaches we are taking to discover and develop novel therapeutics using CRISPR/Cas9 systems are unproven and may never lead to marketable products. If we are unable to develop viable product candidates, achieve regulatory approval for any such product candidate or market and sell any product candidates, we may never achieve profitability.

We are focused on developing curative medicines utilizing the CRISPR/Cas9 genome editing technology. Although there have been significant advances in the fields of gene therapy, which typically involves introducing a copy of a gene into a patient's cell, and genome editing in recent years, CRISPR-based genome editing technologies are relatively new, and their therapeutic utility is largely unproven. The CRISPR/Cas9 technologies that we intend to develop have not yet been clinically tested by us, and we are not aware of any clinical trials for safety or efficacy having been completed by third parties involving these technologies. The scientific evidence to support the feasibility of developing products based on these technologies is both preliminary and limited. Successful development of products by us will require solving a number of issues, including developing or obtaining technologies to safely deliver a therapeutic agent into target cells within the human body or modify human cells while outside of the body such that the modified cells can have a therapeutic effect when delivered to the patient, optimizing the efficacy and specificity of such products, and ensuring the therapeutic selectivity and efficacy of such products. There can be no assurance we will be successful in solving any or all of these issues.

We have principally concentrated our research efforts to date on bringing CRISPR/Cas9 therapeutics to the clinic for various initial indications, and our future success is highly dependent on the successful development of CRISPR-based genome editing technologies, cellular delivery methods and therapeutic applications for these indications. These indications are the principal focus of our initial development efforts, and we may decide to alter or abandon these programs as new data become available and we gain experience in developing CRISPR/Cas9-based therapeutics. We cannot be sure that our CRISPR/Cas9 technologies will yield satisfactory products that are safe and effective, scalable or profitable in our selected indications or any other indication we pursue.

Public perception and related media coverage of potential therapy-related efficacy or safety issues, including adoption of new therapeutics or novel approaches to treatment, as well as ethical concerns related specifically to genome editing and CRISPR/Cas9, may adversely influence the willingness of subjects to participate in clinical trials, or if any therapeutic is approved, of physicians and patients to accept these novel and personalized treatments. Physicians, health care providers and third-party payors often are slow to adopt new products, technologies and treatment practices, particularly those that may also require additional upfront costs and training. Physicians may not be willing to undergo training to adopt these novel and personalized therapies, may decide the particular therapy is too complex or potentially risky to adopt without appropriate training, and may choose not to administer the therapy. Further, due to health conditions, genetic profile or other reasons, certain patients may not be candidates for the therapies. In addition, responses by the U.S., state or foreign governments to negative public perception, ethical concerns or financial considerations may result in new legislation or regulations, or medical standards, that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. Based on these and other factors, health care providers and payors may decide that the benefits of these new therapies do not or will not outweigh their costs.

Our ability to generate product revenue is dependent on the success of our application of CRISPR/Cas9 technology for human therapeutic use, which is at an early stage of development and will require significant additional discovery efforts, preclinical testing and clinical studies, as well as applicable regulatory guidance for preclinical testing and

clinical studies from the FDA and other regulatory authorities, before we can seek regulatory approval and begin commercial sales of any potential product candidates.

Our ability to generate product revenue is highly dependent on our ability to obtain regulatory approval of and successfully commercialize one or more of our product candidates. Any product candidates we discover will require preclinical, clinical and regulatory review and approval in each jurisdiction in which we intend to market the

products, substantial investment, access to sufficient commercial manufacturing capacity and significant marketing efforts before we can generate any revenue from product sales. Before obtaining marketing approval from regulatory authorities for the sale of a product candidate, we must conduct extensive clinical trials to demonstrate the safety, purity and potency, as well as the effectiveness of the product candidates in humans. We cannot be certain that any of our product candidates will be successful in clinical trials and, even if successful, they may not receive regulatory approval.

Our approach to developing therapies for genetic and viral-based diseases centers on using the CRISPR/Cas9 technology to introduce or remove genetic information in vivo to treat various disorders, or to modify human cells ex vivo to create therapeutic cells that can be introduced into the human body to address the underlying disease. Because these are new therapeutic approaches, discovering, developing and commercializing our product candidates subject us to a number of challenges, including:

- obtaining regulatory approval from the FDA and other regulatory authorities that have very limited or no experience with the clinical development of CRISPR/Cas9 therapeutics;
- seeking and obtaining regulatory approval from the FDA and other regulatory authorities in light of no formal guidance regarding potential regulatory pathways for this category of in vivo therapeutics, including preclinical and clinical requirements for approval of an IND;
- educating medical personnel regarding the potential benefits and side effect profile of each of our product candidates;
- developing processes for the safe administration of these products, including long-term follow-up for all patients who receive treatment with any of our product candidates;
- sourcing clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates;
- developing a manufacturing process and distribution network with a cost of goods that allows for an attractive return on investment; and
- establishing sales and marketing capabilities in anticipation of and after obtaining any regulatory approval to gain market acceptance.

Additionally, because our in vivo technology involves gene editing across multiple cell and tissue types, we are subject to many of the challenges and risks that gene therapies face, including:

- regulatory guidance regarding the requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. To date, no products that involve the in vivo genetic modification of patient cells have been approved in the U.S. and a limited number have been approved in the EU;
- improper insertion of a gene sequence into a patient's chromosome could lead to cancer, other aberrantly functioning cells or other diseases, including death;
- the FDA recommends a follow-up observation period of 15 years or longer for all patients who receive treatment using gene therapies, and we may need to adopt such an observation period for our product candidates; and
- clinical trials using therapies that genetically modify cells conducted at institutions that receive funding for recombinant DNA research from the NIH, may be subject to review by the RAC. Although the FDA decides whether individual protocols may proceed, the RAC review process can impede the initiation of a clinical trial, even if the FDA has reviewed the study and it has become effective under an IND.

Further, because our ex vivo product candidates involve gene editing human cells and then manufacturing and delivering modified cells to patients, we are subject to many of the challenges and risks that cell therapies face, including:

- clinical trials using genetically modified cells conducted at institutions that receive funding for recombinant DNA research from the NIH, may be subject to review by the RAC. Although the FDA

- decides whether individual protocols may proceed, the RAC review process can impede the initiation of a clinical trial, even if the FDA has reviewed the study and it has become effective under an IND; and
- clinical trials using engineered cell therapies require unique products to be created for each patient and such individualistic manufacturing may be both inefficient and cost-prohibitive.

To date, although human clinical trials for other in vivo genome editing-based therapeutics have been authorized by the FDA, neither we nor any other company has received regulatory approval in the U.S. or EU to commence human clinical trials utilizing in vivo CRISPR/Cas9-based therapeutics or to market in vivo therapeutics utilizing any genome editing technology, including CRISPR/Cas9. There is no certainty that the FDA or EMA will apply to CRISPR/Cas9 product candidates the same regulatory pathway and requirements it is applying to other in vivo genome editing-based therapeutics; and the FDA and other regulatory authorities have not yet provided written guidance regarding preclinical or clinical studies or regulatory approval pathways specific for in vivo genome editing-based therapeutics. In addition, if any product candidates encounter safety or efficacy problems, developmental delays, regulatory issues or other problems, our development plans and business could be significantly harmed. Further, competitors that are developing in vivo products with similar technology may experience problems with their product candidates or programs that could in turn cause us to identify problems with our product candidates and programs that would potentially harm our business.

Further, significant uncertainty exists regarding the future scope and effect of the FDA's regulatory framework, in particular relating to the review and approval of human therapeutic products because the current U.S. administration and federal legislators have publicly declared their intention to significantly modify the current legal framework governing the FDA. Any such changes to the FDA requirements could impact our ability to obtain approval for our products or sell them profitably. In addition, in the EU, the decision of the United Kingdom to withdraw from the European Union has required the EMA to relocate to the Netherlands, and recruit and retain new personnel to review and approve our submissions for regulatory approval in Europe. EMA's relocation could result in delays and other changes that may impact the timing and our ability to obtain approval for our products. Also, upon exiting the EU, the United Kingdom may enact legislation related to the approval and oversight of human therapeutics in that nation. Until any such legislation is enacted, we will be uncertain as to its effects on our business, including our ability to seek and obtain approval for our products in the United Kingdom.

In addition, during fiscal year 2017, non-commercial entities have commenced human trials involving in vivo CRISPR/Cas9-based therapeutics in China. Neither these entities nor the Chinese regulatory agencies have shared publicly any specific any information on the regulatory process for clinical trial approval including any specific protocol requirements. Any specific requirement from the Chinese regulatory agencies may impact our ability to submit or obtain approval for our products in China. Further, if these human trials are unsuccessful, or if they result in significant adverse events, including deaths, there could be a significant impact to the evaluation of our product candidates globally, as well as an increase in negative public opinion.

Even if we obtain regulatory approval of any product candidates, such candidates may not gain market acceptance among physicians, patients, hospitals, third-party payors and others in the medical community.

The use of the CRISPR/Cas9 system as a framework for developing gene editing-based therapies is a recent development and may not become broadly accepted by physicians, patients, hospitals, third-party payors and others in the medical community. A variety of factors will influence whether our product candidates are accepted in the market, including, for example:

- the clinical indications for which our product candidates are approved;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the incidence and severity of any side effects, including off-target editing or immunogenicity;
- product labeling or product insert requirements of the FDA or other regulatory authorities;

- limitations or warnings contained in the labeling approved by the FDA or other regulatory authorities;
- the timing of market introduction of our product candidates;

- availability or existence of competitive products;
- the cost of treatment in relation to alternative treatments;
- the amount of upfront costs or training required for health care providers to administer our product candidates;
- the availability of adequate coverage, reimbursement and pricing by third-party payors and government authorities;
    - patients' ability to access physicians and medical centers capable of delivering any therapies that we develop;
- the willingness of patients to pay out of pocket in the absence of coverage and reimbursement by third-party payors and government authorities;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- relative convenience and ease of administration, including as compared to alternative treatments and competitive therapies;
- any restrictions on the use of our product candidates together with other medications;
- interactions of our product candidates with other medicines patients are taking;
- potential adverse events for any products developed, or negative interactions with regulatory agencies, by us or others in the gene therapy and gene editing fields; and
- the effectiveness of our sales and marketing efforts and distribution support.

Even if our products achieve market acceptance, we may not be able to maintain that market acceptance over time if new products or technologies are introduced that are more favorably received than our products, are more cost effective or render our products obsolete. In addition, adverse publicity due to the ethical and social controversies surrounding the therapeutic in vivo use of CRISPR/Cas9, gene edited modified cells, or other therapeutics mediums, such as viral vectors that we may use in our clinical trials may limit market acceptance of our product candidates. If our product candidates are approved but fail to achieve market acceptance among physicians, patients, hospitals, third-party payors or others in the medical community, we will not be able to generate significant revenue.

Negative public opinion and increased regulatory scrutiny of in vivo CRISPR/Cas9 use, gene editing or gene therapy generally may damage public perception of the safety of any product candidates that we develop and adversely affect our ability to conduct our business or obtain regulatory approvals for such product candidates.

Gene therapy in general, and gene editing in particular, remain novel technologies, with the first gene therapy product being approved in August 2017 in the U.S. and only a limited number of gene therapy products approved to date in the EU. Public perception may be influenced by claims that gene therapy or gene editing, including the use of CRISPR/Cas9, is unsafe or unethical, and gene therapy or gene editing may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians who specialize in the treatment of diseases targeted by our product candidates prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are more familiar and for which greater clinical data may be available. In addition, responses by the U.S., state or foreign governments to negative public perception or ethical concerns may result in new legislation or regulations that could limit our ability to develop or commercialize any product candidates, obtain or maintain regulatory approval or otherwise achieve profitability. More restrictive statutory regimes, government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death, and the FDA recently initiated a clinical hold on a CAR-T cell therapy clinical trial due to patient deaths, and the company developing the therapy ultimately decided to stop the program. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy or gene editing products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity could result in increased government

regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidate.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, if approved, which could make it difficult for us to sell any product candidates or therapies profitably.

The success of our product candidates, if approved, depends on the availability of adequate coverage and reimbursement from third-party payors, including government agencies. In addition, because our product candidates represent new approaches to the treatment of genetic-based diseases, we cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates or assure that coverage and reimbursement will be available for any product that we may develop.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors are critical to new product acceptance.

Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of 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.

In the U.S., no uniform policy of coverage and reimbursement for products exists among third-party payors. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of our gene-modifying products. Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates. Because our product candidates may have a higher cost of goods than conventional therapies, and may require long-term follow up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater. There is significant uncertainty related to insurance coverage and reimbursement of newly approved products. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

Moreover, increasing efforts by governmental and third-party payors in the U.S. and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, cost containment initiatives and additional legislative changes.

We intend to seek approval to market our product candidates in both the U.S. and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the EU, the pricing of

pharmaceutical products, including biologics, is subject to governmental control and other market regulations which could put pressure on the pricing and usage of our product candidates. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for our product candidates and may be affected by existing and future health care reform measures.

Research and development of biopharmaceutical products is inherently risky. We may not be successful in our efforts to use and enhance our gene editing technology to create a pipeline of product candidates, obtain regulatory approval and develop commercially successful products, or we may expend our limited resources on programs that do not yield a successful product candidate and fail to capitalize on potential product candidates or diseases that may be more profitable or for which there is a greater likelihood of success. If we fail to develop product candidates, our commercial opportunity, if any, will be limited.

We have not currently selected any particular product candidates for clinical development. We are at an early stage of development and our technology and approach has not yet led, and may never lead, to any product candidate appropriate for clinical development or any approved or commercially successful products. Even if we are successful in building our pipeline of product candidates, completing clinical development, obtaining regulatory approvals and commercializing product candidates will require substantial additional funding and are prone to the risks of failure inherent in therapeutic product development. Investment in biopharmaceutical product development involves significant risk that any potential product candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval, or become commercially viable.

We cannot provide any assurance that we will be able to successfully advance any product candidates that we discover through the research process. Our research programs may initially show promise, yet fail to yield product candidates for clinical development or commercialization for many reasons, including the following:

- our technology and approach may not be successful in identifying product candidates for clinical development and commercialization;
- we may not be able or willing to assemble sufficient resources to acquire or discover product candidates for clinical development and commercialization;
- animal or other non-human models for the targeted disease may not be appropriate or available to conduct preclinical testing;
- testing in preclinical models may not be predictive of human clinical testing results because species have distinct genomic sequences that may require the use of species-specific guides and reagents;
- our product candidates may not succeed in preclinical or clinical testing;
- our planned risk mitigation strategy for selecting our initial indications may fail or we may not be able to efficiently apply learnings from our initial development programs to future development programs;
- we may be unable to optimize the therapeutic efficiency, specificity, or selectivity of our future product candidates;
- our therapeutic delivery systems may fail so that even a product candidate with therapeutic activity might not demonstrate a clinically meaningful therapeutic effect;
- a product candidate may not demonstrate in patients the biological, chemical and pharmacological properties identified in laboratory and preclinical studies, or they may interact with human biological systems in unforeseen, ineffective or even harmful ways;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- the therapeutic effect of a product candidate may not be permanent and may diminish over time;
- a single treatment course may not be sufficient for a cure or therapeutic benefit, and it may take several treatment courses for the product to be effective;

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- a well-defined and achievable pathway to regulatory approval may never materialize for a specific product candidate;
- competitors may develop alternatives that render our product candidates obsolete, redundant or less attractive;
- product candidates we develop may be covered by third-party or other exclusive rights or may not receive desired regulatory exclusivity, and we may be unable to maintain, expand or protect our intellectual property rights;
- the market for a product candidate may change during our program so that the continued development of that product candidate is no longer reasonable;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all;
- we may be unable to successfully maintain existing collaborations or licensing arrangements or enter into new ones throughout the development process as appropriate; and
- a product candidate may not be accepted as safe and effective by physicians, patients, hospitals, third-party payors and others in the medical community.

If any of these events occur, we may be forced to abandon our development efforts for a product candidate, program or programs, or we may not be able to identify, discover, develop or commercialize product candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Because we have limited financial and managerial resources, we are initially focused on specific research programs. As a result, we may fail to capitalize on other viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases that may later prove to have greater commercial potential, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights. For additional information regarding the factors that will affect our ability to achieve revenue from product sales, see the risk factor entitled “We have never generated any revenue from product sales and our ability to generate revenue from product sales and become profitable depends significantly on our success in a number of factors.”

If we do not successfully develop and commercialize product candidates based upon our approach, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price. Further, our current focus on CRISPR/Cas9 technology for developing products as opposed to multiple, more proven technologies for product development increases the risk associated with our business. If we are not successful in developing a product candidate using CRISPR/Cas9 technology, we may not be able to successfully implement an alternative product development strategy.

Results, including positive results, from our initial pre-clinical studies are not necessarily predictive of our other ongoing and future pre-clinical and clinical studies, and they do not guarantee or indicate the likelihood of approval of any potential product candidate by the FDA, EMA or any other regulatory agency. If we cannot replicate the positive results from any of our pre-clinical or clinical studies, we may be unable to successfully develop, obtain regulatory approval for and commercialize any potential product candidate.

There is a high failure rate for product candidates progressing through pre-clinical and clinical studies. Even if we are able to successfully complete our ongoing and future pre-clinical studies for any potential product candidate, we may not be able to replicate any positive results from these or any other studies in any of our future pre-clinical and clinical trials, and they do not guarantee approval of any potential product candidate by the FDA, EMA or any other necessary regulatory authorities in a timely manner or at all. Companies in the pharmaceutical and biotechnology industries have commonly suffered significant setbacks in clinical studies after achieving positive results in early stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings made before, during and after clinical studies were underway, or observations regarding the lack of safety or efficacy made in clinical studies, which could include new or previously unreported adverse events. In addition, regulatory delays or rejections may be encountered as a result of many

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factors, including changes in the relevant laws, regulations or regulatory policy during the period of product development.

Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in such studies nonetheless failed to obtain FDA, EMA or other necessary regulatory agency approval. If we fail to obtain results in our on-going, planned and future pre-clinical and clinical studies sufficient to meet the requirements of the relevant regulatory agencies, the development timeline and regulatory approval and commercialization prospects for any potential product candidate, and, correspondingly, our business and financial prospects, would be materially adversely affected.

The reported results of our non-human primate studies are based on top-line interim data and may ultimately differ from actual results once additional data are received and fully evaluated.

The reported results of the non-human primate studies that we have publicly disclosed, and that are discussed herein and in documents we incorporated by reference, consist of top-line interim data. Top-line interim data are based on a preliminary analysis of currently-available data from an ongoing series of studies, and therefore the reported results, findings and conclusions related to these data are subject to change following a comprehensive review of the more extensive data that we expect to receive related to the studies. Our reported results and related top-line interim data are based on assumptions, estimations, calculations and information currently available to us, and we have not received or had an opportunity to fully evaluate all of the data related to the studies. As a result, the top-line interim data results that we have reported may differ from future results, or different conclusions or considerations may qualify such results, once the current data or additional data have been received and fully evaluated. In addition, third parties, including regulatory agencies, may not accept or agree with our assumptions, estimations, calculations or analyses, or may interpret or weigh the importance of data differently, which could impact the value of our technology, the approvability or commercialization of product candidates and our business in general. If the top-line interim data that we have reported related to non-human primate differ from actual results or is perceived as insufficient or faulty, our ability to obtain approval for, and commercialize, our products may be harmed, which could harm our business, financial condition, operating results or prospects.

Clinical development involves a lengthy and expensive process, with an uncertain outcome. We may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of any product candidates.

All of our lead programs are still in the discovery or preclinical stage, and their risk of failure is high. It is impossible to predict when or if any of our programs will prove effective and safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of any of our future product candidates in humans. Preclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We may be unable to establish clinical endpoints that applicable regulatory authorities would consider clinically meaningful, and a clinical trial can fail at any stage of testing. The outcome of preclinical testing 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, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

Successful completion of clinical trials is a prerequisite to submitting an NDA or BLA to the FDA, a Marketing Authorization Application to the EMA and similar filings to comparable foreign regulatory authorities, for each product candidate and, consequently, the ultimate approval and commercial marketing of any product candidates. We

do not know whether any of our clinical trials will begin or be completed on schedule, if at all.

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

- regulators, institutional review boards (IRBs) or ethics committees may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable terms with prospective trial sites and prospective contract research organizations (CROs), the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- clinical trials of any product candidates may fail to show safety or efficacy, produce negative or inconclusive results and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials or we may decide to abandon product development programs;
- the number of patients required for clinical trials of any product candidates may be larger than we anticipate, enrollment in these clinical trials may be lower than required by the regulatory agencies or slower than we anticipate, or participants may drop out of these clinical trials or fail to return for post-treatment follow-up at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, or may deviate from the clinical trial protocol or drop out of the trial, which may require that we add new clinical trial sites or investigators;
- we may elect to, or regulators, IRBs or ethics committees may require that we or our investigators, suspend or terminate clinical research or trials for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of preclinical studies and clinical trials of any product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators, IRBs or ethics committees to suspend or terminate the trials, or reports may arise from preclinical or clinical testing of other gene therapies or gene editing based therapies that raise safety or efficacy concerns about our product candidates; and
- the FDA or other regulatory authorities may require us to submit additional data, such as long-term toxicology studies, or impose other requirements before permitting us to initiate or rely on a clinical trial.

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

Our product development costs will increase if we experience delays in clinical testing or marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be

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restructured or will be completed on schedule, or at all. Significant preclinical or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates and may allow our competitors to bring products to market before we do, potentially impairing our ability to successfully commercialize our product candidates and harming our business and results of operations. Any delays in our preclinical or future clinical development programs may harm our business, financial condition and prospects significantly.

Inconclusive results, lack of efficacy, adverse events or additional safety concerns in clinical trials that we or others conduct may impede the regulatory approval process or overall market acceptance of our future product candidates.

Therapeutic applications of gene editing technologies, and CRISPR/Cas9 in particular, for both in vivo products and utilization in engineered cell therapies, are unproven and must undergo rigorous clinical trials and regulatory review before receiving marketing authorization. If the results of our clinical studies or those of any other third parties, including with respect to gene editing technology or engineered cell therapies, are inconclusive, fail to show efficacy or if such clinical trials give rise to safety concerns or adverse events, we may:

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

Additionally, our future product candidates could potentially cause other adverse events that have not yet been predicted and the potentially permanent nature of gene editing effects, including CRISPR/Cas9's effects, on genes or novel cell therapies in the organs of the human body may make these adverse events irreversible. The inclusion of critically ill patients in our clinical studies or those of our competitors may result in deaths or other adverse medical events, including those due to other therapies or medications that such patients may be using. Any of these events could prevent us from achieving or maintaining regulatory approval or market acceptance of our future product candidates and impair our ability to achieve profitability.

We have never generated any revenue from product sales and our ability to generate revenue from product sales and become profitable depends significantly on our success in a number of areas.

We have no products approved for commercial sale, have not generated any revenue from product sales, and do not anticipate generating any revenue from product sales until sometime after we have received regulatory approval for the commercial sale of a product candidate that we discover. Our ability to generate revenue and achieve and retain profitability depends significantly on our success in many areas, including:

- selecting commercially viable product candidates and effective delivery methods;
- completing research, preclinical and clinical development of product candidates;
- obtaining regulatory approvals and marketing authorizations for product candidates for which we complete clinical trials;

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- developing a sustainable and scalable manufacturing process for product candidates, including establishing and maintaining commercially viable supply relationships with third parties and potentially establishing our own manufacturing capabilities and infrastructure;
- launching and commercializing product candidates for which we obtain regulatory approvals and marketing authorizations, either directly or with a collaborator or distributor;
- accurately assessing the size and addressability of potential patient populations;
- obtaining market acceptance of our product candidates as viable treatment options;
- addressing any competing technological and market developments;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter or which may be necessary for us to develop, manufacture or commercialize our product candidates;
- maintaining good relationships with our collaborators and licensors;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- avoiding infringement of or obtaining licenses to any valid intellectual property owned or controlled by third parties; and
- attracting, hiring and retaining qualified personnel.

Even if one or more product candidates that we discover and develop are approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate and the timing of such costs may be out of our control. Our expenses could increase beyond expectations if we are required by the FDA or other regulatory agencies, domestic or foreign, to change our manufacturing processes or assays, or to perform clinical, nonclinical or other types of additional studies. If we are successful in obtaining regulatory approvals to market one or more product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price and whether we own the commercial rights for that territory. If the number of our addressable disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. If we are not able to generate revenue from the sale of any approved products, we may never become profitable.

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

The biotechnology and pharmaceutical industries, including the gene editing field and cell therapies, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

Competitors in our efforts to provide genetic therapies to patients can be grouped into at least three sets based on their product discovery platforms:

- genome editing companies focused on CRISPR/Cas9 including: Casebia Therapeutics, CRISPR Therapeutics, Inc., Editas Medicine, Inc., ToolGen, Inc. and Tracr Hematology Limited;
- other genome editing companies including: bluebird bio, Inc., Cellectis S.A., Homology Medicines, Inc., Poseida, Inc., Precision BioSciences, Inc. and Sangamo Therapeutics, Inc.; and
- genome therapy companies developing in vivo or ex vivo therapies, such as cell therapies, including: bluebird bio, Inc., Cellectis S.A., Celgene Corporation (which acquired Juno Therapeutics, Inc.), Gilead Sciences, Inc. (which acquired Kite Pharma, Inc.), Novartis A.G. and Spark Therapeutics, Inc.

Our competitors will also include companies that are or will be developing other genome editing methods as well as small molecules, biologics, in vivo gene therapies, ex vivo cell therapies and nucleic acid-based therapies for the same indications that we are targeting with our CRISPR/Cas9-based therapeutics.

Any advances in gene therapy, cell therapies or gene editing technology made by a competitor may be used to develop therapies that could compete against any of our product candidates. Many of these competitors have substantially greater research and development capabilities and financial, scientific, technical, intellectual property, manufacturing, marketing, distribution and other resources than we do, and we may not be able to successfully compete with them.

To become and remain profitable, we must discover, develop and eventually commercialize product candidates with significant market potential, which will require us to be successful in a range of challenging activities. These activities can include completing preclinical studies and clinical trials of product candidates, obtaining marketing approval for product candidates, manufacturing, marketing and selling products that are approved and satisfying any post-marketing requirements. Even if we are successful in selecting and developing any product candidates, in order to compete successfully we may need to be first-to-market or demonstrate that our CRISPR/Cas9-based products are superior to therapies based on the same or different treatment methods. If we are not first-to-market or are unable to demonstrate such superiority, any products for which we are able to obtain approval may not be successful. Furthermore, in certain jurisdictions, if a competitor has orphan drug status for a product and if our product candidate is determined to be contained within the scope of a competitor’s orphan drug exclusivity, then approval of our product for that indication or disease could potentially be blocked, for example, for up to seven years in the U.S. and 10 years in the EU.

We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the Company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

We have a very limited operating history, which may make it difficult to evaluate our current business and predict our future performance.

We are very early in our development efforts and all of our lead programs are still in the discovery stage. We were formed in May 2014, have no products approved for commercial sale and have not generated any revenue from product sales. Our ability to generate product revenue or profits, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and even