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, 2019

☐ **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	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	NTLA	The 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 every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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

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

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

Indicate by check mark whether the registrant 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 $741,046,311 as of June 28, 2019 (based on a closing price of $16.37 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 50,507,681 shares of Common Stock, $0.0001 par value per share, outstanding as of February 21, 2020.

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 2020 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, 2019. 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, 2019

Table of Contents

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 negative of 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 these 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, including the anticipated timing of our submission of investigational new drug applications and initiation of clinical studies for transthyretin amyloidosis, our lead* in vivo *indication, and for acute myeloid leukemia, our lead engineered cell therapy indication, and the nomination of candidates for other development programs;*
- *the initiation, timing, progress and results of our research and development programs and future preclinical and clinical studies, including the anticipated timing of nominating a development candidate or an investigational new drug application for hereditary angioedema;*
- *our ability to use a modular platform capability or other strategy to efficiently discover and develop product candidates, including by applying learnings from one program to other programs;*
- *our ability to research, develop or maintain a pipeline of product candidates;*
- *our ability to manufacture or obtain material for our preclinical and clinical studies, and our product candidates;*
- *our ability to advance any product candidates into, and successfully complete, clinical studies, including clinical studies necessary for regulatory approval and commercialization, and to demonstrate to the regulators that the product candidates are safe and effective and that their benefits outweigh known and potential risks for the intended patient population;*
- *our ability to advance our genome editing and therapeutic delivery capabilities;*
- *the scope of protection we are able to develop, establish and maintain for intellectual property rights, including patents and license rights, covering our product candidates and technology;*
- *our ability to operate, including commercializing products, without infringing or breaching the proprietary or contractual rights of others;*
- *the issuance or enforcement of, and compliance with, regulatory requirements and guidance regarding preclinical and clinical studies relevant to genome editing and our product candidates;*
- *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, and 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 with third parties under favorable terms;*

- *our ability to acquire and maintain relevant intellectual property licenses and rights, and the scope and terms of such rights;*
- *any further arbitration, judicial decisions, or negotiations with Caribou Biosciences, Inc. ("Caribou"), regarding the matters addressed in the September 2019 interim award and related decisions issued by the arbitration panel, including the scope of any leaseback-related arrangement and the timing and amount of payment under any such arrangement, as well as the potential to initiate additional arbitration or legal proceedings;*
- *the potential implications and impact that the interim award and related decisions in our arbitration against Caribou, or any future arbitration or judicial decision with or relating to the same, may have on any other intellectual property rights that we hold, as well as Caribou's potential to compete with us in the field of human therapeutics;*
- *our financial performance or ability to obtain additional funding;*
- *developments relating to our licensors, licensees, third-parties from which we derive rights, collaborators, competitors and our industry; and*
- *other risks and uncertainties, including those listed under the caption "Risk Factors."*

All of our express or implied 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 developing curative therapeutics utilizing a biological tool known as CRISPR/Cas9, which stands for Clustered, Regularly Interspaced Short Palindromic Repeats ("CRISPR")/CRISPR associated 9 ("Cas9"). This is a technology for genome editing, the process of altering selected sequences of genomic deoxyribonucleic acid ("DNA"). We believe that CRISPR/Cas9 technology has the potential to transform medicine by editing disease-associated genes with a single treatment course, and that it can also be used to create novel engineered cell therapies that can replace a patient's diseased cells or effectively target various cancers and autoimmune diseases. We are leveraging our leading scientific expertise, clinical development experience and intellectual property ("IP") position to unlock a broad set of therapeutic applications for CRISPR/Cas9 genome editing and to develop a potential new class of therapeutic products.

Our mission is to build a company to develop curative genome editing treatments that can positively transform the lives of people living with severe and life-threatening disease. We believe we can deliver on our mission and provide long-term benefits for all of our stakeholders by focusing on four key elements -

- Develop curative CRISPR/Cas9 based medicines;
- Advance our science to help more patients;
- Foster an environment that is the best place to make therapies; and
- Focus on long-term sustainability.

Our strategy is to build a full-spectrum genome editing company, by leveraging our CRISPR/Cas9 platform across two areas: *in vivo* applications, in which CRISPR/Cas9 is the therapy, delivered to target cells within the body; and *ex vivo* applications, in which CRISPR/Cas9 creates the therapy of engineered human cells.

The breadth of our CRISPR/Cas9 platform and delivery technology allows us to pursue a multitude of therapeutic targets/clinical indications. Specifically, we can target diseases that have the potential to be addressed by directly editing specific genes (i.e., gene knockout, repair, or insertion) as well as diseases that may be targeted by genetically engineered cell therapies. The successful treatment of these disorders may require various types of genome edits, CRISPR/Cas9 elements and DNA templates. We have assembled multiple *in vivo* and engineered cell therapy capabilities into a pipeline that reflects our full-spectrum approach and leverages the modularity inherent in our platform.

Our diversified pipeline includes *in vivo* development programs targeting genetic diseases, including transthyretin amyloidosis ("ATTR"), which we are co-developing with Regeneron Pharmaceuticals, Inc. ("Regeneron"), and hereditary angioedema ("HAE"). Our pipeline also includes *ex vivo* programs consisting of two separate efforts: (1) a set of proprietary programs focused on engineered cell therapies to treat various cancers and autoimmune diseases including our lead *ex vivo* program to target Wilms' Tumor 1 ("WT1") for acute myeloid leukemia ("AML"); and (2) partnered programs developed in collaboration with Novartis Institutes for BioMedical Research, Inc. ("Novartis"), focused on chimeric antigen receptor ("CAR") T ("CAR-T") cells, hematopoietic stem cells ("HSCs"), the stem cells from which all of the various types of blood cells originate, and stem cells in the eye, or ocular stem cells ("OSCs").

CRISPR/Cas9 Technology

CRISPR/Cas9 genome editing technology was derived from an adaptive defense mechanism of bacteria. In 2012, Dr. Jennifer Doudna, one of our scientific co-founders, 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. The Cas9 endonuclease, a key component of CRISPR/Cas9, can be programmed to cut double-stranded DNA at specific locations. A ribonucleic acid ("RNA") molecule, called a guide RNA ("gRNA"), binds to Cas9 and can be programmed to direct the Cas9 enzyme to a specific DNA sequence.

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. Products based on CRISPR/Cas9 technology may be one of two types: products where CRISPR itself constitutes the therapy and the edit occurs *in vivo*, and products where CRISPR is used to create the therapy where the edit occurs *ex vivo*. *In vivo* editing has the potential to provide curative therapeutic options for patients with genetically-based diseases, while *ex vivo* editing has the potential to create cell-based therapies to combat cancer or autoimmune diseases.

Strategy

Our goal is to build a full spectrum, 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 existence of efficient regulatory pathways to approval; 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 Our Proprietary Delivery System. 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 current *in vivo* pipeline opportunities target diseases of the liver, including ATTR and HAE, which we believe we can address using our proprietary lipid nanoparticle ("LNP") delivery system.

Actively Develop and Expand* Ex Vivo *Therapeutic Programs. We are independently researching and developing proprietary engineered cell therapies to treat various cancers and autoimmune diseases, for example using T cell receptor ("TCR")-engineered T cells for immuno-oncology applications, engineered regulatory T cells for autoimmune disorders and other cell types such as engineered induced pluripotent stem cells for these potential applications. Further, we are supporting Novartis' development of CAR-T cell, HSC and OSC therapies.

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 collaboration focusing on HSCs, OSCs and CAR-T cells with Novartis, an industry leader with the first commercially available CAR-T cell product, our ongoing partnership on *in vivo* liver indications with Regeneron, a leader in genetics-driven drug discovery and development, and our research collaboration on engineered T cell therapies with IRCCS Ospedale San Raffaele ("OSR"), Milan, 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 continue to explore accessing external technologies or opportunities to enhance our leadership position in developing innovative therapeutics.

Our Pipeline

Our diversified pipeline includes *in vivo* and *ex vivo* programs. Our *in vivo* programs focus on treating patients that have significant unmet medical needs due to diseases attributable to genes expressed in the liver – ATTR (which we are co-developing with Regeneron) and HAE. Delivery plays a key role in our *in vivo* therapeutic approach. We have shown in animal models that our proprietary LNP delivery technology, which encapsulates the therapeutic Cas9 messenger RNA ("mRNA") and gRNA into LNPs, can systemically deliver these therapeutic components to the liver.

For *ex vivo* applications, our wholly owned programs focus on next-generation, engineered cell therapy solutions that utilize antigen specific TCRs. The cells to be modified *ex vivo* can come from the individual patient (autologous source) or from another individual (allogeneic source). Our goal for the *ex vivo* pipeline is to move from autologous to allogeneic therapies, and from liquid to solid tumors.

We believe our full spectrum approach to *in vivo* and *ex vivo* programs positions us to build a pipeline across a wide range of indications.

The following table summarizes the status of our most advanced programs:

PROGRAM	APPROACH	Research	Candidate Selection	IND-Enabling	Clinical Development	PARTNER
In Vivo: **CRISPR is the therapy**						
NTLA-2001: Transthyretin Amyloidosis	Knockout					Intellia THERAPEUTICS REGENERON
Hereditary Angioedema	Knockout					Intellia THERAPEUTICS
Research Programs	• Knockout • Insertion • Consecutive Edits					Intellia THERAPEUTICS REGENERON**
Ex Vivo: **CRISPR creates the therapy**						
Sickle Cell Disease	HSC					NOVARTIS Intellia*** THERAPEUTICS
NTLA-5001: Acute Myeloid Leukemia	WT1-TCR					Intellia THERAPEUTICS
Solid Tumors	WT1-TCR					Intellia THERAPEUTICS
Undisclosed Programs	Undisclosed					Intellia THERAPEUTICS
Novartis Programs	CAR-T, HSC, OSC	UNDISCLOSED				NOVARTIS Intellia*** THERAPEUTICS

In Vivo *Programs*

Our selection criteria 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 effective treatments are absent, limited or unduly burdensome. Our initial *in vivo* indications target genetic liver diseases, including ATTR and HAE. Our current efforts on *in vivo* delivery focus on the use of LNPs for delivery of the CRISPR/Cas9 complex to the liver.

Transthyretin Amyloidosis ("ATTR") Program

Background

ATTR is a progressive and fatal disorder resulting from deposition of insoluble amyloid fibrils into multiple organs and tissues leading to systemic failure. Blood-borne transthyretin ("TTR") protein is produced by hepatocytes and normally circulates as a soluble homotetramer that facilitates transport of vitamin A, via retinol binding protein, as well as the thyroid hormone, thyroxine. Mutations in the *TTR* gene lead to the production of TTR proteins that are destabilized in their tetramer form. These tetramers more readily dissociate into the monomeric form, and thence to an aggregative form that results in amyloid deposits in tissues. These deposits cause damage in those tissues, resulting in a disorder known as hereditary TTR amyloidosis ("hATTR"). Over 120 different genetic mutations are currently known to cause hATTR.

Deposits of TTR amyloid in the heart, nerves and/or other tissues can lead to diverse disease manifestations, including two main hereditary forms – hATTR with polyneuropathy ("hATTR-PN"), and hATTR with cardiomyopathy ("hATTR-CM"). Typical onset of disease symptoms is during adulthood and can be fatal within 2 to 15 years. Estimates suggest that approximately 50,000 patients suffer from hATTR worldwide.

In addition to the hereditary forms described above, ATTR can also develop spontaneously in the absence of any *TTR* gene mutation. This wild-type ATTR ("wtATTR"), is increasingly being recognized as a significant and often undiagnosed cause of heart failure in the elderly and is the subject of active investigation. Recent estimates suggest that, globally, between 200,000 and 500,000 people may suffer from wtATTR with cardiomyopathy ("wtATTR-CM").

Limitations of Current Treatment Options

Currently, there are two therapies for the treatment of hATTR-PN approved in the United States ("U.S."), and three approved in most major markets outside of the U.S. While these therapies have shown the potential to slow or halt the progression of neuropathic symptoms, and in some patients lead to an improvement in symptoms, their approved prescribing instructions require them to be administered chronically for the life of the patient in order to sustain benefit. Additionally, patient response to these therapies varies. While some patients may experience symptomatic improvement after being treated with these therapies, the disease continues to progress in many of the treated patients, which highlights the continued need for efficacious and potentially curative therapies. At present, there is only one therapy approved for ATTR-CM (including both hATTR-CM and wtATTR-CM) which has shown the ability to improve patient outcomes, though most patients still appear to have the progressive disease. As with the treatments for hATTR-PN, chronic, lifetime dosing is required to sustain the therapeutic effects.

Our Approach

We believe that we can apply CRISPR/Cas9 technology to potentially cure ATTR by employing a knockout edit to disable the *TTR* gene in the liver. We expect this approach to greatly reduce the production of circulating TTR protein levels, which should slow or stop the accumulation of undesired TTR protein in the nerves and the heart, thereby halting disease progression. Using this approach, we aim to address both forms of the disease - hATTR and wtATTR. Current treatments and ongoing clinical trials in hATTR-PN 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. We believe our approach may improve patient outcomes by potentially eliminating defective TTR protein in a single dose, as opposed to life-long therapy. We have assessed delivery of gRNAs directed at the *TTR* gene together with Cas9 mRNA 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 non-human species.

In non-human primate ("NHP") studies, we have demonstrated our ability to reduce circulating TTR protein to estimated therapeutically relevant levels after a single systemic administration of LNPs containing our CRISPR/Cas9 complex. In December 2019, we completed a year-long durability study of our lead LNP formulation, maintaining an average reduction of more than 95% of serum TTR protein after a single dose in NHPs. The data from our various NHP studies has also demonstrated the transient nature of Intellia's proprietary modular LNP delivery system, which was rapidly cleared from circulation, with all CRISPR/Cas9 complex undetectable in blood and liver within ten days of administration.

On August 1, 2019, we announced that we conducted our pre-Investigational New Drug ("IND") meeting with the U.S. Food and Drug Administration ("FDA") and initiated IND-enabling toxicology studies. In addition, we expect to submit an IND application for NTLA-2001, our lead candidate for the treatment of ATTR, in mid-2020 and anticipate dosing the first patients in the second half of 2020. On February 27, 2020, we announced that we remain on track to submit an IND application for NTLA-2001 in mid-2020 and anticipate dosing the first patients in the second half of 2020.

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 primary 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 TTR protein levels in blood. We expect that the results of our preclinical studies, and discussions with the FDA, the European Medicines Agency ("EMA") and other relevant regulatory agencies as well as patient advocacy groups will be important to inform our clinical trial design. Pursuant to our collaboration agreement with Regeneron, we and Regeneron entered into a Co-Development and Co-Promotion ("Co/Co") agreement directed to the first collaboration target, TTR (the "ATTR Co/Co") agreement, under which the parties share development costs and worldwide commercial profits, and for which we are the clinical and commercial lead. Pursuant to the ATTR Co/Co agreement, Regeneron funded approximately 50% of the program's development costs through 2019. Starting June 2020 and thereafter, Regeneron will share approximately 25% of worldwide development costs and commercial profits for the ATTR program. For more information regarding our collaboration with Regeneron, see the section below entitled "**Collaborations - *Regeneron Pharmaceuticals, Inc.*"**

Hereditary Angioedema ("HAE") Program

Background

HAE is a rare genetic disorder characterized by recurrent, painful and unpredictable episodes of severe swelling. The most common areas of the body to develop swelling are the limbs, face, intestinal tract and airway. Minor trauma or stress may trigger an attack but swelling often occurs without a known trigger. Episodes involving the intestinal tract cause severe abdominal pain, nausea and vomiting. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. The disease is caused by increased levels of bradykinin, a protein which leads to swelling. Most patients with HAE have a deficiency of C1 esterase inhibitor ("C1-INH") protein, which normally prevents the unregulated release and buildup of bradykinin. HAE is estimated to affect 1 in 50,000 people, with an estimated 11,000 to 21,500 diagnosed HAE patients in the U.S. and Europe.

Limitations of Current Treatment Options

Currently there are multiple therapies approved to treat HAE, including acute and prophylactic approaches. Acute treatments are used to treat patients who are experiencing an attack. Prophylactic treatments are used to reduce the number of attacks that a patient may experience. Prophylactic treatments have proven to be effective in reducing the number of attacks for most patients, though some patients still experience breakthrough attacks and such treatment options require regular injections which can be associated with significant treatment burden and impact on quality of life.

Our Approach

Using our modular LNP delivery system, we aim to knock out the *kallikrein B1 ("KLKB1")* gene with a single course of treatment to reduce the spontaneous activation of biological pathways responsible for generating bradykinin and thereby ameliorate the frequency and intensity of HAE attacks. We believe *KLKB1* knockout to be safe, as humans with prekallikrein deficiency appear to have no known health effects. In addition, inhibition of kallikrein activity has proven to be a clinically effective approach as a prophylactic treatment for HAE.

In February 2020, we shared data demonstrating that the knockout of *KLKB1* produced in NHPs resulted in a 90% reduction in kallikrein activity following a single dose. The reduction of kallikrein activity observed corresponds to the reduced enzymatic levels in patients that meaningfully impact HAE attack rates (Source: Banerji et al., NEJM, 2017). This kallikrein activity reduction was sustained for at least five months in an ongoing study, in a highly reproducible manner observed across both rodent and NHP studies. We expect to nominate a development candidate for the treatment of HAE in the first half of 2020.

Pursuant to our collaboration agreement with Regeneron and prior to the initiation of IND-enabling studies, Regeneron could opt into a Co/Co agreement directed to our HAE program. If Regeneron opted to enter into such an agreement, the parties would share development costs and worldwide commercial profits, and we would be the clinical and commercial lead. For more information regarding our collaboration with Regeneron, see the section below entitled "**Collaborations - *Regeneron Pharmaceuticals, Inc.*"**

Ex Vivo *Programs*

We are independently researching and developing proprietary engineered cell therapies to treat various oncological and autoimmune diseases, for example TCR-engineered T cells for immuno-oncology applications and engineered regulatory T cells for autoimmune disorders. Our diverse product strategy includes multiple elements. In particular:

- We are exploring non-CAR-T cellular approaches that use immune cells, including T cells expressing recombinant TCRs, for oncology indications. For example, in our existing collaboration with OSR, we have identified optimized TCRs recognizing a tumor target, WT1, that could be used to treat a variety of cancers.
- We seek to develop allogeneic cellular therapies, which are those derived from unmatched donors and modified outside of the human body to allow them to be administered to an unrelated patient.
- We are also exploring methods to apply CRISPR/Cas9 editing to CD4 immune cells to induce a non-reverting regulatory T cell phenotype, to create therapies that address autoimmune diseases.

In addition, our partner Novartis is developing therapies using CAR-T cells for oncology indications, as well as HSC and OSC-based therapies.

Acute Myeloid Leukemia ("AML")

Background

AML includes a heterogenous group of blood cancers arising from the malignant expansion of hematopoietic cells of the myeloid lineage. AML is associated with weakness, fatigue and bleeding resulting from the depletion of healthy myeloid cells, and is typically rapidly progressive and fatal without immediate treatment. AML is an aggressive and hard-to-treat cancer, resulting in less than 30% of patients living more than five years after diagnosis. AML is the most common acute leukemia in adults and is associated with the largest number of annual deaths from leukemia in the U.S. It is estimated that there have been nearly 11,000 deaths due to AML, as well as over 21,000 new AML cases in the U.S. in 2019. While AML can occur at any age, the prevalence of the disease increases with age, resulting in a median age at diagnosis of 67 years.

Limitations of Current Treatment Options

Induction chemotherapy, most commonly with cytarabine and anthracycline, represents the standard first-line treatment option for patients who can tolerate an intensive treatment regimen. Patients who achieve remission with induction typically receive additional chemotherapy or an HSC transplant as consolidation therapy. While this treatment approach has the potential to lead to sustained remission or even cure patients, the intensity of these treatments is associated with significant morbidity and mortality. Patients who are older, who represent a significant proportion of the patient population, are often unable to be treated with an intensive regimen and are commonly treated with lower intensity chemotherapy or hypomethylating agents. While these therapies offer the potential to prolong survival and address some of the clinical symptomatology associated with AML, they are not generally considered to be potentially curative treatments. Even among patients who are considered fit enough to receive an intensive regimen, a significant proportion of patients are refractory (i.e., do not achieve a complete remission). Further, relapse is common even among those patients who achieve a remission. While additional lines of treatment may be possible, cure rates are extremely low among relapsed and refractory patients. Combined, the high percentage of patients who are unable to tolerate an intensive potentially-curative regimen, the high percentage of refractory patients and high relapse rates have led to the low overall survival rate in AML patients.

Over the past several years, new treatments have emerged for AML with different mechanisms of action. While these treatments have led to improvements in response rates and in some cases increased overall survival, the outcomes demonstrated thus far have been incremental in nature and long-term outcomes in AML continue to be extremely poor.

Our Approach

We have nominated NTLA-5001 as our first engineered T cell therapy development candidate for the treatment of AML, utilizing our TCR-directed approach to target the WT1 intracellular antigen. Our WT1-directed TCR T-cell therapy aims to develop a broadly applicable treatment for AML, regardless of mutational background of a patient's leukemia. This approach employs CRISPR/Cas9 complexes to knock out and replace the endogenous TCR with a natural, high affinity therapeutic TCR. The resulting cells are engineered to be capable of specific and potent killing of AML blasts without bone marrow cell toxicity. In February 2020, we presented data demonstrating that the selection of a natural, high-affinity TCR, in combination with our CRISPR-enabled engineering and targeted insertion, results in an engineered T cell capable of specific and potent killing of primary AML blasts. Importantly, our studies showed that CRISPR-enabled engineering overcomes key challenges of traditional TCR approaches, such as mispairing between therapeutic and endogenous TCR, therefore creating a more homogenous T cell product. The cells engineered with our lead WT1 TCR also exhibited no detectable off-target reactivity to bone marrow cells, which express WT1 at low levels. We continue to advance good manufacturing practices ("GMP") manufacturing-related development activities in support of a Phase I clinical trial. We expect to submit an IND application for the use of NTLA-5001 to treat AML in the first half of 2021.

Research Collaboration with Novartis

Under our collaboration agreement with Novartis, we received an upfront technology access payment from Novartis of $10.0 million, and we have received an additional $50.0 million, in aggregate, in additional technology access fees and research payments during the five-year collaboration term. In December 2019, the research term ended, although the 2014 Novartis Agreement remains in effect. Accordingly, Novartis has selected various CAR-T cell, HSC and OSC targets for continued development, for which we will be eligible to receive milestone and royalty payments in the future. Further, 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 collaboration with Novartis, see the section below entitled **"Collaborations - *Novartis Institutes for BioMedical Research, Inc.*"**

CAR-T Cell Program

In 2017, the first CAR-T cell products, including Novartis' *Kymriah*, were approved by the FDA to treat certain oncological indications such as pediatric acute lymphoblastic leukemia and Non-Hodgkins Lymphoma. Additional therapies are being developed for blood cancers such as AML, multiple myeloma and chronic lymphocytic leukemia, as well as several solid-tumor cancers. In CAR-T cell therapy, naturally-occurring immune cells, specifically T cells, are modified *ex vivo* by inserting a CAR into the T cells, thereby redirecting their response towards cancer cells.

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

- 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.
- 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 knock out 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.

Novartis is progressing CRISPR/Cas9-edited CAR-T cells directed to its selected CAR targets. The target selection process was completed by the end of 2019, and all non-selected CAR targets are available for our development.

HSC Program

HSCs are the stem cells from which all of the various types of blood cells originate. The HSCs present in transplanted bone marrow, mobilized peripheral blood or cord blood can repopulate a patient's blood system. There are multiple potential opportunities for treating patients using engineered HSCs, including treating 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; 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. In 2019, Novartis completed IND-enabling studies in support of a potential IND on a program targeting sickle cell disease that leveraged our CRISPR/Cas 9 technology. We are entitled to receive a $5.0 million payment related to this regulatory milestone upon filing the IND. During the research collaboration with Novartis that concluded in December 2019, we pursued a number of potential gene targets and therapeutic indications with Novartis. From those targets, Novartis has selected a limited number of HSC targets for development into human therapeutics. Novartis' ability to select additional HSC therapeutic targets under the agreement expired in December 2019.

OSC Program

In 2018 we announced an expansion of our existing cell therapy collaboration with Novartis to include the *ex vivo* development of innovative cell therapies using certain OSCs. As part of the updated collaboration terms, Novartis obtained the right to develop CRISPR/Cas9-based products for a limited number of targets using these stem cells. We received a one-time $10.0 million cash payment and, consistent with the original collaboration agreement, we are also eligible to receive downstream success-based milestones and royalties. We retained rights to all other *in vivo* and *ex vivo* applications of CRISPR/Cas9, including for eye disorders. Novartis' selection period for additional OSC targets expired in December 2019.

Other Research Programs

We are pursuing a number of *in vivo* and *ex vivo* genome editing programs. Within our *in vivo* research efforts, we continue to work on programs such as primary hyperoxaluria Type 1 ("PH1"), alpha-1 antitrypsin deficiency ("AATD"), and Hemophilia B, which leverage our capabilities to knockout, insert and make consecutive edits to the genome. We are also investigating delivery strategies that target tissues outside of the liver.

Within our *ex vivo* research efforts, we are developing engineered cell therapies to treat a range of hematological and solid tumors. We are pursuing modalities, such as TCR, with broad potential in multiple indications. We continue to advance efforts to move from autologous to allogeneic therapies and from liquid to solid tumors.

Our Platform

An integral part of creating a full-spectrum therapeutic product pipeline based on CRISPR/Cas9 technology is to develop a robust technology platform, based on proprietary and in-licensed technologies. Our modular platform is based on our proprietary components that can serve both *in vivo* and *ex vivo* programs, as well as our delivery technologies that can be used in either program type. In addition to the components described below, we are developing robust, high volume (high throughput) capabilities centering around enabling strategic target identification and validation that we believe will provide us with a competitive advantage in creating successful therapeutic products.

Informatics

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

Guide RNA qualification

As part of the process to identify gRNAs for potential development candidates, we screen numerous gRNAs for their ability to generate the required edit at the genomic site of interest, called on-target activity, as well as any potential 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 gRNAs 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 gRNA 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 gRNAs having a variety of modifications, such as changes to the gRNA sequence or chemical modifications of nucleotides. As part of our development of CRISPR/Cas9 therapeutics, we are engineering modified gRNAs to, for example, improve editing efficiency, specificity and stability inside cells, 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 gRNAs for therapeutic applications.

Nuclease

Our current preferred Cas9 protein is derived from a species 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 bacteria, which may differ from *Spy* Cas9 in aspects such as specificity, size or mechanism of DNA recognition, binding and cutting. We are pursuing these alternative Cas9 forms and other nucleases through ongoing internal work, collaborations with our existing partners and scientific founders and in-licensing opportunities. We also are 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

Knockout

The CRISPR/Cas9 system, by itself, primarily functions to cut DNA, while the resulting desired therapeutic editing events are performed by the cell, subsequent to the cut, as the cell seeks to rejoin the cut ends. One type of edit is caused by a DNA repair mechanism that is prone to losing or adding short lengths of DNA around the cut site. The resulting changes in the DNA impair the function of any encoded protein, causing a knockout edit. Using a combination of our informatics, gRNA qualification and format and nuclease platform capabilities, we have developed an efficient process to identify gRNAs that create this kind of edit at high frequency while possessing high specificity for the on-target site and no substantial off-target effects.

Within both NHP and rodent disease models we have demonstrated the ability to knockout multiple targets in the liver including TTR, *KLKB1*, *SERPINA1*, hydroxyacid oxidase 1 (“*Hao1”)* and lactate dehydrogenase A (“*Ldha”)*. These data demonstrated the modular nature of our propriety LNP delivery system.

Gene Insertion

While knockout edits can be made using solely a Cas9 protein and gRNA, other kinds of editing, involving repair and insertion, additionally require a template DNA that contains a desired genomic sequence that may be inserted or used to correct the original sequence. For *ex vivo* applications, in addition to delivering a Cas9-gRNA complex, the DNA template may be delivered by physical means such as electroporation in combination with a Cas9-gRNA complex, or by other means such as viral vectors or chemical means. For *in vivo* applications, we have developed combination approaches for delivering the editing machinery by LNP, and the repair and insertion templates by adeno-associated virus (“AAV”) vectors. For example, at the 2019 American Society of Gene and Cell Therapy Annual Meeting, we presented initial data from an ongoing study demonstrating the first CRISPR/Cas9-mediated, targeted transgene insertion in the liver of NHPs, using *F9* as a model gene. In August 2019, we announced additional results from the in-life portion of the NHP study. Following a single dose to NHPs of the hybrid LNP-AAV delivery system containing an *F9* DNA template, we demonstrated that the circulating human FIX protein levels achieved in NHPs were at or above normal levels. Additionally, the NHP data expands on the durability of clinically relevant human FIX protein levels achieved in mice for over 12 months. We are currently working closely with Regeneron to move the program forward and are also independently evaluating the hybrid LNP-AAV delivery system for targeted insertion across several other transgenes of interest in an *in vivo* setting.

Consecutive Editing

Consecutive editing is any combination of knockout and insertion strategies. At the 2019 European Society of Gene and Cell Therapy Annual Meeting, we reported the first demonstration of a consecutive *in vivo* gene knockout and insertion in a mouse model of AATD. The consecutive edits led to a greater than 98% reduction of the disease-causing protein and sustained restoration of the missing protein to therapeutically relevant circulating protein levels throughout the study.

In Vivo *Delivery*

We are focusing our initial *in vivo* applications in the liver, where we deliver the CRISPR/Cas9 therapy to patients using our proprietary LNP platform.

LNPs encapsulate the therapeutic cargo, providing it with stability, selective delivery, improved pharmacologic properties and controlled circulation time. Our therapeutic cargo is designed to degrade relatively quickly, resulting in transient expression of Cas9. We see multiple advantages of using LNPs as an *in vivo* delivery vehicle, particularly as optimized by us for delivery of the CRISPR/Cas9 system or its components. First, certain LNPs have historically demonstrated efficacy, safety and favorable tolerability and are currently used as a delivery system for mRNA, as well as small interfering RNA (“siRNA”). mRNA is RNA that encodes proteins and siRNA is RNA that causes the degradation of selected cellular mRNAs. 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 our proprietary LNP delivery system, which uses a set of biodegradable, well-tolerated lipids, based on lipids originally developed by Novartis and in-licensed by us for use with all genome editing technologies, including CRISPR/Cas9 products. To date, we have successfully demonstrated well-tolerated *in vivo* editing in various animal models, including in mouse, rat and NHP livers, with a single dose of systemically delivered LNPs. We also have shown successful delivery to cells in the brains of mice and NHPs and editing in mouse brain cells using CRISPR/Cas9 delivered by direct injection of one of our proprietary LNP formulations.

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 have identified, and continue to investigate, 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 our LNP system 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. We also are developing delivery strategies that we believe will allow us to target other tissues.

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). We use the CRISPR/Cas9 system to perform the modification, and deliver the system using a clinically proven method, electroporation. In human cells, we have been able to achieve robustly high editing efficiency, including rates greater than 90%, of both copies of a single gene (bi-allelic editing), while preserving cell viability. 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.

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.

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. ("Novartis")

In December 2014, we entered into a strategic license and collaboration agreement with Novartis (the "2014 Novartis Agreement"), primarily focused on the research of new *ex vivo* CRISPR/Cas9-edited therapies using CAR-T cells and HSCs. The agreement was amended in December 2018 to also include research on OSCs. In December 2019, per the terms of the 2014 Novartis Agreement, the research term ended, although the 2014 Novartis Agreement remains in effect. As provided in the agreement, Novartis has selected various CAR-T cell, HSC and OSC targets for continued development, for which we will be eligible to receive milestone and royalty payments in the future.

Agreement Structure. Under the 2014 Novartis Agreement, the parties agreed to engage in collaborative research activities using our CRISPR/Cas9 platform to identify and research therapeutic, prophylactic and palliative products and services relating to the following applications: (a) *ex vivo* HSCs and (b) *ex vivo* CAR-T cells. In addition, in the last two years of the collaboration term, Novartis was permitted to engage in research and development of a limited number of *in vivo* targets using our platform.

Scope of Collaboration. During the five-year research term, the parties researched potential therapeutic, prophylactic and palliative *ex vivo* applications of CRISPR/Cas9 technology in HSCs and CAR-T cells. Research expenses incurred by us in support of the collaboration were reimbursed by Novartis.

HSC Program. We and Novartis agreed to collaborate exclusively with each other during the research term to conduct research on *ex vivo* applications of CRISPR/Cas9 technology for HSC targets under a research plan agreed upon by both parties. At the end of the research term in December 2019, this exclusive HSC research collaboration ended. Within the *ex vivo* HSC therapeutic space, Novartis obtained exclusive rights to research and develop human therapeutics for a limited number of HSC targets, which Novartis selected in a series of selection windows. During the research term, we had 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 had the right to research an additional limited number of non-selected HSC targets on a non-exclusive basis, but Novartis did not exercise this right. Because the research term has ended, the parties can no longer select additional exclusive HSC targets, and Novartis has an exclusive license to research, develop and commercialize human therapeutic products directed to its selected HSC targets. Novartis assumed sole responsibility for developing and commercializing human therapeutic products for the HSC targets it selected arising from our collaboration and is solely responsible for the costs and expenses of developing, manufacturing and commercializing its HSC products. To maintain its exclusive license on a target-by-target basis, Novartis is required to use commercially reasonable efforts to research, develop and commercialize at least one HSC product directed to each of their selected HSC targets. In 2019, Novartis announced that it had completed IND-enabling studies in support of a potential IND on a program targeting sickle cell disease that leveraged our CRISPR/Cas 9 technology.

CAR-T Program. We and Novartis also agreed to collaborate exclusively with each other during the research term on research directed to applying CRISPR/Cas9 technology to CAR-T cell targets under a research plan agreed upon by both parties. At the end of the research term in December 2019, this exclusive research collaboration ended. Under the 2014 Novartis Agreement, Novartis assumed sole responsibility for developing human therapeutic products for the limited number of CAR targets it selected arising from our collaboration and is solely responsible for the costs and expenses of developing, manufacturing and commercializing its selected targets. Novartis has an exclusive license to research, develop and commercialize CAR products directed to its selected CAR-T cell targets. To maintain its exclusive license on a target-by-target basis, Novartis is required to use commercially reasonable efforts to research, develop and commercialize at least one CAR-T cell product directed to each of its selected CAR targets.

Governance. The parties formed HSC and CAR-T cell steering committees with responsibility for oversight of these respective research programs and approval of the associated research plans. Beginning in December 2018, the HSC steering committee also became responsible for the OSC program (see the section below entitled *"2018 Amendment to the Agreement")*. These steering committees in turn were overseen by a joint steering committee and comprised an equal number of representatives from each party. The steering committees terminated upon completion of the research term in December 2019.

Financial Terms. We received an upfront technology access payment from Novartis of $10.0 million in January 2015 and were 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. To date, we have received $20.0 million in technology access fees and $20.0 million in research payments related to these programs. In addition, for each Novartis product under the collaboration (whether it is an HSC or CAR-T cell product, and beginning in December 2018, an OSC product), 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 IND 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 U.S. and 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. In 2019, Novartis completed IND-enabling studies in support of a potential IND on a program targeting sickle cell disease leveraging our CRISPR/Cas 9 technology for which we are entitled to a $5.0 million milestone payment upon filing of the IND.

Equity Investments. Additionally, at the inception of the arrangement at which time Intellia was a privately-held company, Novartis invested $9.0 million to purchase our Class A-1 and Class A-2 Preferred Units (the "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.

License Grant to Novartis. In the 2014 Novartis Agreement, we granted to Novartis a license to our CRISPR/Cas9 platform technology, including a sublicense to certain platform rights licensed from Caribou Biosciences, Inc. ("Caribou"), that is exclusive in the *ex vivo* 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 CRISPR-edited products directed to such targets.

License Grant to Intellia. In the 2014 Novartis Agreement, prior to the Novartis Amendment described below, Novartis granted us a non-exclusive license to its IP covering a small molecule for HSC expansion and its LNP platform technology to research, develop and commercialize HSC and *in vivo* genome editing products, respectively.

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

2018 Amendment to the Agreement. In December 2018, we entered into an amendment to this agreement with Novartis (the "Novartis Amendment") which expanded the scope of the 2014 Novartis Agreement to include the *ex vivo* development of CRISPR/Cas9-based cell therapies using limbal stem cells, a type of OSC, primarily against gene targets selected by Novartis. In connection with the Novartis Amendment, we received a one-time payment of $10.0 million in December 2018. The governance, license rights and development responsibilities, as well as milestones and royalties, associated with any OSC program and product follow those for the HSC programs and products. Because the research term has ended, as with the HSC programs, the parties' exclusive research collaboration for limbal stem cells has ended, and Novartis has an exclusive license to research, develop and commercialize OSC products directed to a limited number of OSC targets. As part of the Novartis Amendment, Intellia's license to Novartis' LNP technology was expanded to include use in all genome editing applications in both *in vivo* and *ex vivo* settings.

Term and Termination. The term of the 2014 Novartis 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) ten 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 IP 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 and continuing obligations. 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. ("Regeneron")

In April 2016, we entered into a license and collaboration agreement with Regeneron (the "Regeneron Agreement").

Agreement Structure. The Regeneron Agreement has two principal components: (i) a product development component under which the parties will research, develop and commercialize CRISPR/Cas-based therapeutic products primarily focused on genome editing in the liver, and (ii) a technology collaboration component, pursuant to which the parties will engage in research and development activities aimed at discovering and developing novel technologies and improvements to CRISPR/Cas technology to enhance our genome editing platform. Under the Regeneron 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.

Scope of Collaboration. Under the terms of the six-year research collaboration, Regeneron may obtain exclusive rights for up to ten targets to be chosen by Regeneron during the collaboration term subject to a target selection process and various adjustments and limitations set forth in the agreement. Of these ten total targets, Regeneron may select up to five non-liver targets, while the remaining targets must be focused in the liver. Certain non-liver targets from Intellia's ongoing and planned research at the time, as well as any targets included in another Intellia collaboration, were excluded from this collaboration. At the inception of the agreement, Regeneron selected the first of its ten targets, ATTR, which is subject to a Co/Co agreement between us and Regeneron, the general terms and conditions for which were outlined within the Regeneron Agreement.

Research Collaboration. 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 its selected liver targets, and Regeneron will be responsible for preclinical research and conducting clinical development, manufacturing and commercialization of products directed to each of its exclusive targets. 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 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.

Reserved Liver Targets. We retain the exclusive right to solely develop products via CRISPR/Cas genome editing directed against certain specified genetic targets. During the collaboration term and subject to a 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 during the term may be subject to further Co/Co agreements at our or Regeneron's option, as applicable, which either can exercise pursuant to defined conditions.

Governance. Under the Regeneron Agreement, the parties formed a joint steering committee, which is responsible for setting research objectives and overseeing the general strategies and research and development activities undertaken by the parties. Additionally, under the ATTR Co/Co, the parties formed a Joint Development and Commercialization Committee ("JDCC") to oversee all profit share products under the Co/Co agreement as discussed below. The JDCC has responsibility for overseeing the development, manufacture, regulatory matters and commercialization (including pricing and reimbursement) of ATTR, as the first profit share product under the Regeneron Agreement.

Financial Terms. We received a nonrefundable upfront payment of $75.0 million. In addition, on Regeneron programs that are not subject to Co/Co agreements we may be eligible to earn, on a per-licensed target basis, (i) up to $25.0 million in development milestones, including for the dosing of the first patient in each of Phase I, Phase II and Phase III clinical trials; (ii) up to $110.0 million in regulatory milestones, including for the acceptance of a regulatory filing in the U.S., and for obtaining regulatory approval in the U.S. and in certain other identified countries; and (iii) up to $185.0 million in sales-based milestone payments. 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 incorporate our existing low- to mid-single-digit royalty obligations under a license agreement with Caribou.

Equity Investments. In connection with this collaboration, Regeneron purchased $50.0 million of our common stock in a private placement under a Stock Purchase Agreement concurrent with our initial public offering.

Term and Termination. The research collaboration term ends in April 2022, except that Regeneron may make a one-time payment of $25.0 million to extend the term for an additional two-year period. The Regeneron 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 Regeneron 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 or 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 IP revert to us, as described in the agreement. Following such termination, we may owe Regeneron royalties, in certain circumstances, up 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 Regeneron Agreement either in its entirety or with respect to the research collaboration or one or more of the targets selected by Regeneron, in the event of the other party's uncured material breach.

Co-Development and Co-Promotion Agreement. In July 2018, we and Regeneron finalized the form of the Co/Co agreement that will be used as the basis for each Co/Co agreement directed to a target. Simultaneously, we and Regeneron executed the Co/Co agreement directed to the first collaboration target, ATTR, for which we are the clinical and commercial Lead Party (see below) and Regeneron is the Participating Party (see below).

Co-Development and Co-Promotion: Agreement Structure. Under the Regeneron Agreement, Regeneron has the right to exercise up to at least five options to enter into a Co/Co agreement for our liver targets (other than Intellia's reserved liver targets), while we may exercise at least one option to enter into a Co/Co agreement for Regeneron's liver targets, the exact number of options being subject to certain conditions of the target selection process. Each option to enter into a Co/Co agreement must be exercised (or forfeited) once a target reaches a defined preclinical stage. Within 15 days of exercising the option, the party exercising the option must pay $1.5 million to the other party as compensation for prior work. The ATTR program was exempted from this payment. One party will be the "Lead Party" and the other party the "Participating Party". The Lead Party shall have control and primary responsibility for the development, manufacturing, regulatory and commercial activities. The Participating Party shall have the right to consult on these activities through its participation on the JDCC and will have the right to co-fund development and commercialization activities in exchange for a share of profits. In general, under each Co/Co agreement, the parties will share equally in worldwide development costs and profits of any future products. Prior to reaching a specific development milestone, the Participating Party may elect to reduce its share of worldwide development costs and profits by 50%.

Pursuant to the ATTR Co/Co, Regeneron was obligated to fund 50% of the research and development costs for the ATTR program. On December 13, 2019, Regeneron informed us that it would exercise its rights under the ATTR Co/Co to modify its share of worldwide development costs and commercial profits for the ATTR program from 50% to 25%, effective six months after its notice.

Co-Development and Co-Promotion: Termination. Either party may terminate by providing 180 days written notice. If Intellia terminates, the product becomes a Regeneron product, and is subject to all future milestone and royalty payment obligations under the Regeneron Agreement. If Regeneron terminates and has contributed at least $5.0 million in development costs under the Co/Co agreement, Intellia will pay low- to mid-single digit royalties on the net sales of the product, depending on co-funding percentage, stage at termination and, if any, incorporation of Regeneron's IP into the product.

IRCCS Ospedale San Raffaele ("OSR"), Milan

In June 2017, we entered into a collaboration and license option agreement with Ospedale San Raffaele, Milan (the "OSR Agreement"). The research collaboration between the parties involves identifying new WT1 TCRs, editing T cells with CRISPR/Cas9 to knockout the endogenous TCR and insert a WT1 TCR, and testing the engineered T cells to assess their ability to attack tumors, particularly AML and solid tumors, that express WT1. Generally, OSR is responsible for identifying, characterizing and testing new WT1-specific TCRs, and we are responsible for developing and providing CRISPR/Cas9 reagents, methods and other technologies for editing T cells. We have the exclusive right to use the IP developed under the collaboration to develop therapeutic products. Discoveries from this collaboration are included in our first *ex vivo* product candidate directed to AML, which we refer to as NTLA-5001. The parties are researching additional engineered WT1 TCR T cells as therapies for other types of cancer, including those caused by solid tumors. The OSR Agreement also granted us an option to obtain an exclusive license to certain patent families of OSR and IP developed in the collaboration to research, develop and commercialize engineered WT1 TCR T cells comprising the WT1 TCRs identified by OSR in the collaboration. In December 2019, we exercised this option.

We will also owe OSR a royalty below 1% on net sales of licensed products sold by us and a share in the low- to mid-single digit percentage of sublicense revenue that we receive if we sublicense our rights under the OSR Agreement to a third party. The research collaboration ends in June 2020, except that it may be extended by the parties. The OSR 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**.**

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 IP because we:

- have built, and intend to expand, a broad worldwide portfolio of IP, including patents and patent applications, in areas relevant to the development and commercialization of human therapeutic products using CRISPR/Cas9 technology;
- protect our IP 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 IP rights, including, for example, through the use of copyright protection, trademark and regulatory protections 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 genome editing, improvement modifications of these CRISPR systems, LNP technologies, TCRs for specific targets, and cell expansion technology relevant to stem cell-based therapies. We access these patent estates from licensors including Caribou, Novartis and OSR. 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 IP relevant to our targeted therapeutic programs and platforms and to develop and acquire new IP in collaboration with third parties.

In addition to our in-licensed IP, our IP portfolio includes over 30 patent families filed since 2015 covering solely or jointly owned technologies that we have developed independently or through our collaborations with Novartis, Regeneron and OSR. The patent families claim inventions relating to CRISPR/Cas9 improvements, methods for delivering CRISPR/Cas9 complexes, methods of treating diseases using CRISPR/Cas9 genome editing, and methods for analyzing editing events, among others. Patents resulting from our internal portfolio, if issued, would expire no earlier than 2036.

We 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 IP relevant to our targeted therapeutic programs and platforms and to develop and acquire new IP in collaboration with third parties.

Caribou Biosciences In-Licensed Intellectual Property ("Caribou")

In July 2014, we entered into a license agreement with Caribou (the "Caribou License"), 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 IP 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 International ("Pioneer") 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 IP 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 IP 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 IP included in the license agreement amounting to a total of $4.3 million paid through December 31, 2019. 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 January 30, 2018. Caribou, which is obligated to pay a portion of our patent filing, prosecution and maintenance costs for any such licensed IP, also has an option to sublicense any CRISPR/Cas9 IP in-licensed by us for uses and activities in its retained field of use.

The Caribou License grants us sublicenses in our field of use to IP 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 IP 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, 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 and through the IP cutoff date, Caribou filed over 50 patent applications in the U.S. 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.

On October 17, 2018, we initiated an arbitration proceeding against Caribou asserting that Caribou is violating the terms and conditions of the Caribou License, as well as other contractual and legal rights, by using and seeking to license to third parties two patent families relating to specific structural or chemical modifications of gRNAs, that were purportedly invented or controlled by Caribou, in our exclusive human therapeutic field. Under the Caribou License, Caribou granted to us a worldwide, exclusive license to all of Caribou's IP relating to CRISPR/Cas9 technology for all therapeutic, prophylactic and palliative uses and applications for any or all diseases and conditions in humans, with the sole exceptions of anti-microbial and/or anti-fungal applications. The license encompassed all CRISPR/Cas9 IP developed or controlled by Caribou as of July 16, 2014 and through January 30, 2018 that was necessary or useful for us to develop, manufacture or commercialize products in our field, as well as any technology developed by Caribou under a service agreement entered into by us and Caribou in July 2014. Caribou has asserted that the two families of IP are outside the scope of our license. In accordance with the Caribou License, we submitted a demand for arbitration seeking a declaration that the disputed IP is included within the scope of our license under the Caribou License, an award of compensatory, consequential and punitive damages based on Caribou's conduct, and an injunction prohibiting Caribou from licensing or using this IP in our exclusive human therapeutics field, among other claims.

On September 26, 2019, we announced that the arbitration panel issued an interim award concluding that both the structural and chemical gRNAs modification technologies were exclusively licensed to us by Caribou pursuant to the Caribou License. After concluding that the chemical modification technology was within the scope of our exclusive license from Caribou, the arbitration panel nevertheless noted that its decision could delay or otherwise adversely impact the development of these modified gRNAs as human therapeutics. It also noted that we currently are not using these modified gRNAs in any of our active programs. Thus, solely with respect to the particular modified gRNAs, the arbitration panel stated that it will declare that Caribou has an equitable "leaseback", which it described as exclusive, perpetual and worldwide (the "Caribou Award"). The panel instructed the parties to negotiate the terms of the Caribou Award, including Caribou's future payments to us for the same, but the parties' negotiations reached an impasse.

On February 6, 2020, after considering additional submissions from the parties, the panel clarified that the Caribou Award is limited to a particular on-going Caribou program, which seeks to develop a CAR-T cell product directed at CD19. The panel instructed the parties to seek to negotiate terms based on this scope. Accordingly, the Caribou Award will be subject to terms, including Caribou's future payments to us to be negotiated by the parties or, if unsuccessful, adjudicated in additional arbitration or judicial proceedings.

Pursuant to the September 2019 interim award, the Caribou Award by the panel does not include the structural guide modifications IP at issue in the arbitration, any other IP exclusively licensed or sublicensed by Caribou to us under the Caribou License (including but not limited to the foundational CRISPR/Cas9 IP co-owned by the Regents of the University of California, University of Vienna and Dr. Emmanuelle Charpentier), or any other of our IP.

Upon, and subject to the terms of, a final award, which will follow further arbitration or legal proceedings and potential additional negotiations between the parties, Caribou could be able to use the modified gRNAs at issue for CAR-T cell human therapeutics directed at CD19. Either we or Caribou may challenge the arbitration panel's decisions under limited circumstances.

Other than with regards to the technologies in dispute, the interim award has no effect on our rights or Caribou's obligations under the Caribou License. The interim award has no impact on any of our current programs, although it could impact the 2014 Novartis Agreement.

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, 2019, this family includes granted patents in many jurisdictions outside the U.S., 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 IND 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 U.S., 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/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" or the "Broad"), which claim aspects of CRISPR/Cas9 systems and methods to edit genes in eukaryotic cells, including human cells. An interference is an adversarial proceeding conducted by the USPTO's Patent Trial and Appeal Board (the "PTAB") to determine the initial inventor of a particular invention claimed in U.S. patents and patent applications owned by different parties. On January 11, 2016, the PTAB declared an interference involving one UC/Vienna/Charpentier application, 12 Broad issued patents and a Broad patent application. In the order declaring the interference, the PTAB designated UC/Vienna/Charpentier the "Senior Party" and the Broad the "Junior Party". In March 2016, the PTAB re-declared the interference to add an additional U.S. patent application owned by the Broad. On February 15, 2017, the PTAB dismissed the proceeding finding that the parties' respective patent claims involved in the interference were distinct such that they did not meet the legal requirement to proceed with the interference. Specifically, the PTAB concluded that the Broad's claims were directed to the use of CRISPR/Cas9 only in eukaryotic cells and, thus were patently distinct from UC/Vienna/Charpentier's claims, which were directed to the use of CRISPR/Cas9 in all settings. 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 ("the Federal Circuit") seeking a review and reversal of the PTAB's decision. On September 10, 2018, the Federal Circuit affirmed the PTAB's decision to terminate the interference proceeding. The time for UC/Vienna/Charpentier to ask for a rehearing by the Federal Circuit or permission from the U.S. Supreme Court to appeal has expired. Accordingly, the Federal Circuit returned the UC/Vienna/Charpentier patent application at issue in the terminated interference to the USPTO. On February 8, 2019, the USPTO issued a notice allowing the patent application, which, when issued, will cover generally the use of the CRISPR/Cas9 technology using a single RNA guide in any setting, including cellular settings. On June 25, 2019, PTAB of the USPTO declared an interference between the UC/Vienna/Charpentier eukaryotic patent family and the Broad Institute patent family to determine which research group first invented the use of the CRISPR/Cas9 technology in eukaryotic cells and, therefore, is entitled to the patents covering the invention. On August 26, 2019, the PTAB redeclared the interference to include additional UC/Vienna/Charpentier patent applications covering the invention that had also been found allowable by the USPTO. As of January 31, 2020, the interference involves 14 allowable patent applications from the UC/Vienna/Charpentier eukaryotic patent family and 13 patents and one patent application from the Broad Institute patent family. If it were to succeed in the interference, the Broad could seek to assert its issued patents against us based on our CRISPR/Cas9-based activities, including commercialization. Through the end of 2019, apart from the interference the USPTO has issued or allowed over 20 patents to UC/Vienna/Charpentier covering compositions and methods of use of the CRISPR/Cas9 technology.

Pioneer Hi-Bred International (DuPont Company) Intellectual Property

Pioneer Hi-Bred International 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 IP, 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 IP 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

The 2014 Novartis Agreement grants us worldwide, non-exclusive, royalty-free rights to a portfolio of 14 Novartis patent families containing granted patents and pending applications in the U.S. and internationally relating to LNP compositions, methods of use and modified nucleic acids. The license under the 2014 Novartis Agreement permits us to use the Novartis LNPs to develop therapeutic, prophylactic, and palliative CRISPR-based *in vivo* products. Under a December 2018 amendment to the 2014 Novartis Agreement, we obtained rights to use these LNPs both *in vivo* and *ex vivo* for any genome editing product. 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, under the 2014 Novartis Agreement, 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 the 2014 Novartis Agreement, any platform IP developed as part of the collaboration is owned solely by us, while all other IP developed within the collaboration, including product-based IP, is jointly owned by us and Novartis. We cannot guarantee that IP 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 IP we license under our agreement with Caribou for the Novartis-selected HSC and CAR-T cell 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.

In December 2018, we entered into an amendment to our agreement with Novartis which expands the scope of the 2014 Novartis Agreement to include the *ex vivo* development of CRISPR/Cas9-based cell therapies using limbal stem cells primarily against selected gene targets by Novartis.

Manufacturing

We have entered into certain manufacturing and supply arrangements with third-party suppliers to support production of our product candidates and their components. We plan to continue to rely on these qualified third-party organizations and our own capabilities 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 *in vivo* product 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 manufacturing facilities or continue to rely on third parties to manufacture commercial quantities of any products that we may successfully develop. In certain instances, we may consider building our own commercial infrastructure.

Competition

The biotechnology and pharmaceutical industries are extremely competitive in the race to develop new products. While we believe we have significant competitive advantages with our industry-leading expertise in genome editing, clinical development expertise and dominant IP 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 large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions. 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 based technologies including: Beam Therapeutics Inc., Caribou Biosciences, Inc., CRISPR Therapeutics, Inc., Editas Medicine, Inc., ToolGen, Inc., Tracr Hematology Limited and Verve Therapeutics, Inc.;
- other genome editing companies including: Allogene Therapeutics, Inc., 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: Asklepios Biopharmaceutical, Inc., bluebird bio, Inc., Cellectis S.A., Bristol Myers Squibb (which acquired Celgene Corporation), Gilead Sciences, Inc. (which acquired Kite Pharma, Inc.), Novartis A.G., Roche Holding AG (which acquired Spark Therapeutics, Inc.) and Voyager 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, engineered cell therapies (both autologous and allogeneic) and nucleic acid-based therapies for the same indications that we are targeting with our CRISPR/Cas9-based therapeutics.

Government Regulation and Product Approval

As a biopharmaceutical company, we are subject to extensive legal and regulatory requirements. For example, we may need approval from regulatory agencies for our nonclinical and clinical studies, development, manufacturing, distribution, exportation and importation, commercialization, marketing and reimbursement relating to our products and product candidates. Relevant regulatory authorities include, but are not limited to, the FDA, the EMA, the Commission of the European Union, EU member state agencies, such as Germany's Federal Institute for Drugs and Medicinal Devices ("BfArM"), and other countries' similar agencies, such as the United Kingdom Medicines and Healthcare Products Regulatory Agency ("MHRA").

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 other information, and the IND must become effective before clinical trials may begin.

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 biological products, including gene and cell therapies. CBER's Office of Tissues and Advanced Therapies ("OTAT") is responsible for oversight of gene therapy and related products, and the Cellular, Tissue and Gene Therapies Advisory Committee ("CTGTAC") advises CBER on its reviews. Human gene therapy products are defined as all products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and *ex vivo* genetically modified human cells. FDA has published guidance documents related to, among other things, gene therapy products in general and their preclinical assessment, potency or other quality testing, and chemistry, manufacturing and control information in gene therapy INDs, and long-term adverse event monitoring of clinical trial subjects; 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 guidances pertaining to Regenerative Medicine Advanced Therapies, which are defined as including cell therapy, therapeutic tissue engineering products, human cell and tissue products and combination products using any such therapies or products. Additionally, 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 number of guidances have been revised to reflect the growing knowledge and incorporation of newer technology, including certain considerations for genome editing. A small, but growing number of gene therapy products have been approved by regulatory agencies. In 2012, the EMA authorized the marketing of the first gene therapy product approved by regulatory authorities anywhere in the Western world. And in the U.S., in 2017, the FDA approved the first two cell-based, gene therapy products as well as a gene therapy product. Additional gene therapies have been approved in the U.S. in both 2018 and 2019.

Ethical, social and legal concerns about genome-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 guidances changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Gene and Cell Therapy Products Development Process

The FDA approves biologics, including gene and cellular therapy products, 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 a BLA for marketing approval that includes substantial evidence of 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 BLA; and
- FDA review and approval of the BLA licensure.

Before testing any drug or biological product candidate, including gene and cellular therapy product candidates, 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.

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. The FDA may also impose clinical holds on a 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 National Institutes of Health ("NIH") Guidelines for Research Involving Recombinant DNA Molecules.

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 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 up to 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 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 also are 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 biologics such as gene and cellular therapy products, 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 also are 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 genome 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, 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.

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 to support a BLA. 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 biological product candidate (such as gene and cellular therapy products), FDA approval of a BLA must be obtained before commercial marketing of the product. The 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"), a BLA or supplement to a 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 of 2012 ("FDASIA") requires that a sponsor who is planning to submit a marketing application for a 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 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 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 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 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 the BLA to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission, 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 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 BLA must submit a proposed REMS; the FDA will not approve the application without a REMS, if required.

Before approving a 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 are adequate to assure consistent production of the product within required specifications. Additionally, before approving a 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 GCP 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 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 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 VI (Fiscal Years 2018-2022) 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, also known as a Major Amendment, within the last three months before the PDUFA goal date.

Orphan Drug Designation

The FDA may grant Orphan Drug Designation to biological products, including cellular and gene therapy 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 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 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

In the U.S. and the EU, as well as in other countries, there are a number of programs to expedite development, review and approval of products for serious or life-threatening disease or condition that address an unmet medical need in the relevant regulatory jurisdiction. In the U.S., these FDA programs include Fast Track Designation, priority review, accelerated approval and breakthrough designation. Similar programs in the EU include accelerated assessment, conditional approval and PRIME, which stands for priority medicines.

The FDA's Fast Track program intends to expedite or facilitate the process for reviewing new drug and biological products that meet certain criteria. Specifically, new 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 biologic, including gene and cellular therapy products, may request that the FDA designate the product as a Fast Track product at any time during the product's clinical development, but ideally not later than the 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.

In the U.S., 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. 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 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 or biological product 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.

Orphan designation, 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 and, as applicable, their counterparts in other jurisdictions, requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products, including gene and cellular therapy 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, quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products, including gene and cellular therapy 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.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products, including gene and cellular therapy products, in the U.S. 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 BLA, including withdrawal of the product from the market, as well as potential civil and criminal liability. 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.

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" or "ACA"), 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 in the U.S. 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 and Privacy Laws

In addition to FDA restrictions on marketing of 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 laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, individuals or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or certain rebates), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement for or recommendation of the purchase, lease, order, arrangement for any good, facility, item or service, for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act ("FCA"). Violators are subject to civil and criminal fines and penalties, as well as imprisonment and exclusion from government healthcare programs;

- federal civil and criminal false claims laws, including, without limitation, the federal FCA, and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from the federal government, including Medicare, Medicaid and other government payors, that are false or fraudulent or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or to avoid, decrease or conceal an obligation to pay money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims by, for example, promoting a product off-label. The FCA also permits a private individual acting as a "whistleblower" to bring civil whistleblower or *qui tam* actions against individuals (including biopharmaceutical manufacturers and sellers) on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery. These laws impose criminal and civil penalties on violators;
- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), and its implementing regulations, which impose criminal and civil liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. HIPAA violations can lead to civil and criminal liability;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH"), and their respective implementing regulations, which impose, among other things, requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, 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 attorneys' fees and costs associated with pursuing federal civil actions. In addition, state and non-U.S. laws govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same requirements, thus complicating efforts to comply with their respective provisions;
- the U.S. federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act," created under the ACA, and their implementing regulations, which require manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually, to the Centers for Medicare and Medicaid Services ("CMS"), information related to payments or other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare providers, and teaching hospitals, as well as ownership and investment interests held by physicians, other healthcare providers, and their immediate family members. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately, and completely reported in an annual submission. Effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers, such as physician assistants and nurse practitioners;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- the Foreign Corrupt Practices Act ("FCPA") and other laws which prohibit improper payments or offers of payments to foreign governments and their officials and political parties by U.S. persons and issuers as defined by the statute for the purpose of obtaining or retaining business;
- the FD&C Act, which prohibits, among other things, the commercialization of adulterated or misbranded drugs and medical devices and the PHS Act, which prohibits, among other things, the commercialization of biological products unless a biologics license is in effect; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and may be broader in scope than their federal equivalents; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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

In the event we decide to conduct clinical trials or enroll subjects in our future clinical trials, we may be subject to additional privacy restrictions. As of May 25, 2018, the General Data Protection Regulation ("GDPR") regulates the collection, use, storage, disclosure, transfer or other processing of personal data, including personal health data, in the EU. The GDPR covers any business, regardless of its location, that provides goods or services to residents in the EU and, thus, could incorporate our activities in EU member states. The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for "sensitive information," which includes health and genetic information of individuals residing in the EU, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedies in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the EU to regions that have not been deemed to offer "adequate" privacy protections, such as the U.S. currently. Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU member states, which may deviate slightly from the GDPR, may result in warning letters, mandatory audits and financial penalties, including fines of up to 4% of annual global revenues, or €20,000,000, whichever is greater. As a result of the implementation of the GDPR, we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules, including as implemented by individual countries. Further, the United Kingdom's exit from the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated, and what other aspects of EU privacy laws will be adopted, rejected or modified by the United Kingdom. Additionally, California recently enacted the California Consumer Privacy Act ("CCPA"), which creates new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA will require covered companies to provide new disclosure to consumers about such companies' data collection, use and sharing practices, provide such consumers new ways to opt-out of certain sales or transfers of personal information, and provide consumers with additional causes of action. The CCPA went into effect on January 1, 2020, and the California Attorney General will commence enforcement actions for violations beginning July 1, 2020. The California Attorney General has proposed draft regulations, which have not been finalized to date, that may further impact our business activities if they are adopted. The uncertainty surrounding the implementation of CCPA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information.

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, individual imprisonment, and additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with this law, 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.

Regulation in the European Union

In the European Union, medicinal products, including advanced therapy medicinal products, ("ATMP"s), are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products, which are cells or tissues that have undergone substantial manipulation and that are administered to human beings in order to regenerate, repair or replace a human tissue. We anticipate that our gene therapy development products would be regulated as ATMPs in the EU.

To obtain regulatory approval of an investigational product under EU regulatory systems, we must submit a marketing authorization application ("MAA"). The application used to submit the BLA in the U.S. is similar to that required in the EU, with the exception of, among other things, region-specific document requirements. The EU also provides opportunities for market exclusivity. For example, in the EU, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. Data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic or biosimilar application during the eight year period. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity period. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be an innovative medicinal product, and products may therefore not qualify for data exclusivity. Products with an orphan designation in the EU will, upon the grant of a marketing authorization for an orphan product, receive ten years of market exclusivity, during which time no "similar medicinal product" for the same indication may be placed on the market. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. An orphan product can also obtain an additional two years of market exclusivity in the EU where an agreed Pediatric Investigation Plan ("PIP") for pediatric studies has been complied with. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the U.S. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as an orphan medicinal product if it is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting no more than five in 10,000 persons in the EU when the application is made; or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

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

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

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

Pediatric development

In the EU, companies developing a new medicinal product must agree upon a PIP with the EMA, and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The MAA for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Post-approval controls

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports ("PSUR"s).

All new MAAs must include a risk management plan ("RMP"), describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved Summary of Product Characteristics and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each EU member state and can differ from one country to another.

Other Government Regulation

In addition to the healthcare laws and regulations in the U.S. and EU discussed above, we may be subject to a variety of regulations in these and other jurisdictions governing, among other things, animal research, clinical studies, manufacture, marketing approval, and any commercial sales and distribution of biological 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 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, health maintenance organizations, private health insurers and other organizations.

In the U.S., no uniform policy of coverage and reimbursement for biological products, including gene and cellular therapy products, exists among third-party payors. As a result, obtaining coverage and reimbursement approval for such 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 regarding the products' clinical benefits and risks 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, and health care providers may not prescribe, our product candidates unless coverage is provided, and reimbursement is adequate to cover a significant portion of the product's cost to the patient. 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. 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 biological products and, as a result, they may not cover or provide adequate payment for our product candidates. In addition, we expect to experience pricing pressures in connection with the sale of any of our product candidates upon their approval due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, cost containment initiatives and additional legislative changes. For these reasons, there is significant uncertainty related to coverage and reimbursement of our future 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.

Third-party and government payors are increasingly reducing reimbursements for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our products or a decision by a third-party payor to not cover our products could reduce physician usage of the products and have a material adverse effect on our sales, results of operations and financial condition.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA") established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress.

It is likely that our product candidates, once approved, will have to be administered by a health care provider. Under currently applicable U.S. law, certain products not usually self-administered (including injectable drugs) may be eligible for coverage under Medicare Part B. As a condition of receiving Medicare Part B reimbursement, the manufacturer of the therapy is required to participate in other government healthcare programs, including the Medicaid Drug Rebate Program and the 340B Drug Pricing Program, both of which require the manufacturer to provide rebated pricing under certain conditions. For example, the Medicaid Drug Rebate Program requires pharmaceutical manufacturers to have a national rebate agreement with the federal government as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Under the 340B Drug Pricing Program, the manufacturer must extend discounts to program eligible entities, which generally are federally funded clinics and hospitals that serve large numbers of low-income and uninsured patients.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product, or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the U.S. and generally prices tend to be significantly lower.

Healthcare Reform

In the U.S. and some foreign jurisdictions, there have been, and likely will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system directed at broadening the availability of healthcare, improving the quality of healthcare, and containing or lowering the cost of healthcare.

For example, in March 2010, the ACA was enacted in the U.S. The ACA includes measures that have significantly changed, and are expected to continue to significantly change, the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA of greatest importance to the pharmaceutical industry are that the ACA:

- subjects biological products to potential competition by biosimilars;
- made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs to 23.1% of average manufacturer price ("AMP"), and adding a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP;
- imposed a requirement on manufacturers of branded drugs to provide a 50% (increased to 70% on January 1, 2019 pursuant to subsequent legislation) point-of-sale discount off the negotiated price of branded drugs dispensed to Medicare Part D beneficiaries in the coverage gap (i.e., "donut hole") as a condition for a manufacturer's outpatient drugs being covered under Medicare Part D;
- extended a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expanded the entities eligible for discounts under the 340B Drug Discount Program;
- established a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected;
- imposed an annual, nondeductible fee and tax on any entity that manufactures or imports certain branded prescription drugs, apportioned among these entities according to their market share in certain government healthcare programs;
- imposed new reporting requirements on drug manufacturers for payments made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in significant civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission; and
- established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. The research conducted by the Patient-Centered Outcomes Research Institute may affect the market for certain pharmaceutical products. The ACA established the Center for Medicare and Medicaid Innovation ("CMMI") within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding was allocated to support the mission of CMMI through 2019. Pursuant to the Fiscal Year 2020 budget, CMMI will receive funding for 10 more years.

Congress also could consider additional legislation to repeal, replace, or further modify elements of the ACA. Thus, the full impact of the ACA, or any law replacing elements of it, and the political uncertainty regarding any repeal and replacement on the ACA, on our business remains unclear.

Additionally, there have been a number of proposed regulatory actions and legislative recommendations aimed at lowering prescription drug prices. In May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option to use step therapy, a type of prior authorization, for Part B drugs. This final rule codified CMS's policy change that was effective January 1, 2019.

We cannot predict what healthcare reform initiatives may be adopted in the future. Further federal, state and foreign legislative and regulatory developments are likely, and we expect ongoing initiatives to increase pressure on drug pricing. Such reforms could have an adverse effect on anticipated revenues from product candidates and may affect our overall financial condition and ability to develop product candidates.

Employees

As of February 21, 2020, we had 270 full-time employees, 208 of whom were primarily engaged in research and development activities and approximately 73 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").

The SEC maintains an Internet website that contains reports, proxy and information statements, and other information regarding us and other issuers that file electronically with the SEC. The SEC's Internet website address is http://www.sec.gov.

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, 2019 and in other documents that we file with the SEC, in evaluating us 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 us. 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 the Discovery, Development, Manufacturing and Commercialization of Product Candidates

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, including *in vivo* therapies and engineered cell therapies. Although there have been significant advances in recent years in the fields of gene therapy, which typically involves introducing a copy of a gene into a patient's cells, and genome editing in recent years, *in vivo* CRISPR-based genome editing technologies are relatively new, and their therapeutic utility is largely unproven. In addition, even though cell therapy products have been developed and received regulatory approval in key jurisdictions, such as the United States ("U.S.") and European Union ("EU"), no genome editing *in vivo* therapy or genome-edited engineered cell therapy has been approved, and the potential to successfully obtain approval remains unproven.

The CRISPR/Cas9 therapies, whether *in vivo* or engineered cell therapies, 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 CRISPR/Cas9-based therapies. The scientific evidence to support the feasibility of developing *in vivo* products or engineered cell therapies based on the CRISPR/Cas9 technology 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 engineer 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, efficacy, potency, purity and safety 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-based 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 on-going 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 efforts and technologies will yield satisfactory products that are safe and effective, sufficiently pure or potent, manufacturable, scalable or profitable in our selected indications or any other indication we pursue. We cannot guarantee that progress or success in developing any particular CRISPR/Cas9 therapeutic product will translate to other CRISPR/Cas9 products.

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 potentially 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, 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 and manufacturing capabilities, as well as applicable regulatory guidance regarding preclinical testing and clinical studies from the U.S. Food and Drug Administration ("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 and clinical activities and studies, regulatory review and approval in each jurisdiction in which we intend to market the products, substantial investment, establishing manufacturing capabilities, 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 efficacy, of the product candidates in humans. We cannot be certain that we will be successful on any of these endeavors, or that any of our product candidates will be successful in clinical trials and, even if successful, that we will receive regulatory approval.

Our approach to developing therapies centers on using the CRISPR/Cas9 technology to alter, introduce or remove genetic information *in vivo* to treat various disorders, or to engineer 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, manufacturing 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, and which may require additional significant testing or data compared to more traditional therapies;
- seeking and obtaining regulatory approval from the FDA and other regulatory authorities in light of no formal regulatory guidance for CRISPR/Cas9-based *in vivo* therapeutics, including preclinical and clinical requirements for clearance of an Investigational New Drug application ("IND") and, as appropriate thereafter, a Biologics License Application ("BLA"), or corresponding applications outside the U.S.;
- educating medical personnel, including clinical investigators, and patients 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;
- establishing process development and manufacturing capabilities that can produce sufficient clinical and, if approved, commercial quantities of product candidates in accordance with the FDA and other relevant regulatory agencies' requirements;
- 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 authorization.

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

- regulatory guidance regarding the requirements governing gene and genome editing therapy products have changed and may continue to change in the future. To date, only a limited number of products that involve *in vivo* gene transfer have been approved globally;
- improper modulation of a gene sequence, including insertion of a sequence into a patient's chromosome, could lead to cancer, other aberrantly functioning cells or other diseases, including death;
- transient expression of the Cas9 protein within patients' cells could lead to patients having an immunological reaction towards those cells, which could be severe or life-threatening;
- corrective expression of a missing protein in patients' cells could result in the protein being recognized as foreign, and lead to a sustained immunological reaction against the expressed protein or expressing cells, which could be severe or life-threatening; and
- regulatory agencies may require extended follow-up observation periods of patients who receive treatment using genome editing products, including for example the FDA's recommended 15-year follow-up observation period for these patients, and we will need to adopt such observation periods for our product candidates if required by the relevant regulatory agency, which could vary by country or region.

Further, because our *ex vivo* product candidates involve editing human cells and then delivering modified cells to patients, we are subject to many of the challenges and risks that engineered cell therapies face. For example, clinical trials using engineered cell-based gene therapies may require unique products to be created for each patient and such individualistic manufacturing may be both inefficient and cost-prohibitive.

To date, only a few human clinical trials utilizing either *in vivo* or *ex vivo* CRISPR/Cas9-based therapeutics have been authorized in the U.S. and EU member states. Further, only a limited number of human clinical trials for *in vivo* therapies or engineered cell therapies developed using other genome-editing technologies have been authorized by the FDA in the U.S. or by the relevant regulatory agencies in the EU member states. There is no certainty that the FDA or the EMA will apply to CRISPR/Cas9 product candidates the same regulatory pathway and requirements it is applying to other *in vivo* therapies or *ex vivo* engineered therapeutics; and the FDA and other regulatory authorities have not yet provided specific written guidance regarding preclinical or clinical studies or regulatory approval for either *in vivo* or *ex vivo* genome editing-based therapeutics. In addition, if any product candidates encounter safety or efficacy problems, development delays, regulatory issues or other problems, our development plans and business could be significantly harmed. Further, competitors that are developing *in vivo* or *ex 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.

Also, uncertainty exists regarding the future scope and effect of the FDA's application of its regulatory framework to CRISPR/Cas9 therapies, 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 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. 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.

Results, including positive results, from our initial preclinical activities and studies are not necessarily predictive of our other ongoing and future preclinical 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 preclinical or clinical activities and studies, we may be unable to successfully develop, obtain regulatory approval for and commercialize any potential product candidate.

There is a high failure rate, as well as potential substantial and unanticipated delays, for product candidates progressing through preclinical and clinical studies. Even if we are able to successfully complete our ongoing and future preclinical and clinical activities and studies for any potential product candidate, we may not be able to replicate, or may have to engage in significant efforts and resource and time investments to replicate, any positive results from these or any other studies in any of our future preclinical 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 or delays 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 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 preclinical and clinical activities and 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.

Negative public opinion and increased regulatory scrutiny of CRISPR/Cas9 use, genome 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 genome editing in particular, remain novel technologies, with only a limited number of gene therapy products approved to date in the U.S. and EU. Public perception may be influenced by claims that gene therapy or genome editing, including the use of CRISPR/Cas9, is unsafe or unethical, or carries an undue risk of side effects, such as improper insertion of a gene sequence into a patient's chromosome could lead to cancer, and gene therapy or genome 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. Serious adverse events such as these in our clinical trials, or other clinical trials involving gene therapy or genome 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. In addition, the use of the technology by third parties in areas that are not being pursued by us, such as for targeting and editing of embryonic cells, could adversely impact public and governmental perceptions regarding the ethics and risks of the CRISPR/Cas9 technology and lead to social or legal changes that could limit our ability to apply the technology to develop human therapies addressing disease. For example, reports of the use of CRISPR/Cas9 in China and Russia to edit embryos *in utero* has generated and may continue to create negative public perception about the use of the technology in humans. Negative public and governmental perception of the technology, or additional governmental regulation of our technologies, could also adversely affect our stock price or our ability to enter into revenue generating collaborations or obtain additional funding from the public markets.

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 genome editing technologies, and CRISPR/Cas9 in particular, for both *in vivo* products and 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 genome 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 Risk Evaluation and Mitigation Strategy ("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 genome 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.

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 a 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;

- regulatory agencies may require us to perform more extensive or lengthier clinical testing compared to existing therapeutic modalities;
- 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, or not available in a reasonable timeframe;
- 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 genome 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 the 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 the 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 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.

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 genome editing field and engineered 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: Beam Therapeutics Inc., Caribou Biosciences, Inc. ("Caribou"), CRISPR Therapeutics, Inc., Editas Medicine, Inc., ToolGen, Inc., Tracr Hematology Limited and Verve Therapeutics, Inc.;
- other genome editing companies including: Allogene Therapeutics, Inc., bluebird bio, Inc., Cellectis S.A., Homology Medicines, Inc., Poseida, Inc., Precision BioSciences, Inc. and Sangamo Therapeutics, Inc.; and
- gene therapy companies developing *in vivo* or *ex vivo* therapies, such as cell therapies, including: Asklepios Biopharmaceutical, Inc., bluebird bio, Inc., Cellectis S.A., Bristol Myers Squibb (which acquired Celgene Corporation), Gilead Sciences, Inc. (which acquired Kite Pharma, Inc.), Novartis A.G., Roche Holding AG (which acquired Spark Therapeutics, Inc.) and Voyager Therapeutics, Inc.

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

Any advances in gene therapy, engineered cell therapies or genome 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, manufacture 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 at a sufficient scale, marketing and selling products that are approved and satisfying any pre-approval, approval and 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 commercially 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 our value and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

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

We may not be able to initiate or continue clinical trials for any future product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the U.S. If patients are unwilling to participate in our clinical studies because of concerns about, or negative publicity from, adverse events in the genome editing, gene therapy or engineered cell therapy fields, the novel nature of the CRISPR/Cas9 genome editing technology, the irreversibility of the effects of CRISPR/Cas9 or for other reasons, including competitive clinical studies for similar patient populations, then the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical studies altogether. In addition, any patients who would otherwise be eligible for clinical trials that we may hold may instead enroll in clinical trials of product candidates of our competitors.

Patient enrollment is affected by other factors including:

- the size, location and nature of the patient population;
- the severity of the disease under investigation;
- the patient eligibility criteria for the study in question;
- the perceived risks and benefits of the product candidate under study;
- the design of the clinical trial;
- the availability of alternative treatments;
- our payments for conducting clinical trials;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in clinical trials may result in increased development costs for any of our potential future product candidates, which would cause our value to decline and limit our ability to obtain additional financing. Furthermore, we expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials, and, while we expect to enter into agreements governing their committed activities, we will have limited influence over their actual performance.

Research and development of biopharmaceutical products is inherently risky. We may not be successful in our efforts to use and enhance our genome editing technology to create a pipeline of product candidates, establish the necessary manufacturing capabilities, 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.

Although we have selected an initial product candidate for clinical development for our transthyretin amyloidosis ("ATTR") program, 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 deemed appropriate for clinical development by a regulatory agency or any approved or commercially successful products. Even if we are successful in building our pipeline of product candidates, completing clinical development, establishing the necessary manufacturing processes and capabilities, 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 deemed appropriate 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;
- progress made in one target or using one editing approach may not translate to any other target or editing approach;
- 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 not replicate the results from earlier studies or 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;
- we may not be able to sufficiently control the effect of a product candidate to gain regulatory approval;
- 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;
- our product candidates may not be sufficiently well-tolerated for either one-time or repeat treatments necessary for maximum effectiveness;
- 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;

- we may be unable to manufacture the product candidates after transferring our manufacturing processes from our research and development facilities to larger-scale facilities operated by either a contract manufacturing organization ("CMO") or by us, as well as delays or failure by our CMOs or us to make any changes to such manufacturing process to meet specifications for the product candidates' specifications;
- a product candidate may not be capable of being produced in clinical and, if approved, 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, manufacture 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 areas."

If we do not successfully develop, manufacture 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.

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 genome 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 any unintended DNA changes;
- 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 government authorities and other third-party payors;
- 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 government authorities and other third-party payors;
- 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 genome 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. Our efforts to educate the health care providers, patients and third-party payors about our products may require significant resources and may never be successful.

If, in the future, we are unable to establish sales, marketing and distribution capabilities or enter into agreements with third parties to sell, market and distribute products based on our technologies, we may not be successful in commercializing our products if and when any product candidates or therapies are approved and we may not be able to generate any revenue.

We do not currently have a sales, marketing or distribution infrastructure and, as a company, have no experience in the sale, marketing or distribution of therapeutic products. To achieve commercial success for any approved product candidate for which we retain sales and marketing responsibilities, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. In the future, we may choose to build a focused sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, some of our product candidates if they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

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

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product candidates that we may develop;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;
- the location of patients in need of our product candidates and the treating physicians who may prescribe the products; and
- unforeseen costs and expenses, as well as legal and regulatory requirements, associated with creating and operating a sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market and sell any product candidates that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates. Further, our business, results of operations, financial condition and prospects will be materially adversely affected.

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. There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products, particularly gene editing and engineered cell products. Coverage may be more limited than the purposes for which a therapeutic is approved by the FDA or comparable foreign regulatory authorities. 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 other third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. In the U.S., the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services ("CMS"), an agency within the U.S. Department of Health and Human Services. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare, and private payors often follow CMS' coverage decisions.

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 maintain pricing sufficient 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 and the United Kingdom, 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.

In vivo ***genome editing products and*** **ex vivo** ***engineered cell therapies based on CRISPR-Cas9 genome editing technology are novel and may be complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development, approval or commercialization of our product candidates or otherwise harm our business.***

The manufacturing process used to produce CRISPR/Cas9-based *in vivo* and engineered cell therapy product candidates may be complex, as they are novel and have not been validated for clinical and commercial production and may require components that are difficult to obtain or manufacture at the necessary quantities and in accordance with regulatory requirements. Several factors could cause production interruptions, including equipment malfunctions; facility unavailability or contamination; raw material cost, shortages or contamination; natural disasters; disruption in utility services; human error; insufficient personnel; inability to meet legal or regulatory requirements; or disruptions in the operations of our suppliers.

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

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

Further, certain of our product candidates may require components that are unavailable or difficult to acquire or manufacture at the necessary scale and in compliance with regulatory requirements to support our clinical trials or, if approved, commercial efforts. In addition, we may have to rely on third-party CMOs to manufacture these components and the final product candidates. We may not have full control of these CMOs and they may prioritize other customers or be unable to provide us with enough manufacturing capacity to meet our objectives. Even if we decide to manufacture the product candidates or their components ourselves, we may face extremely high costs and long timelines to build and maintain manufacturing facilities. We may rely on CMOs outside the U.S. for certain components of our product candidates, and may be subject to importation regulations that may affect our ability to manufacture or increase the cost of our product candidates.

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

Any problems in manufacturing processes or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs.

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

We are increasingly dependent upon information technology systems, infrastructure, and data to operate our business. In the ordinary course of business, we collect, store, and transmit large amounts of confidential information (including but not limited to intellectual property, proprietary business information, and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party vendors who may or could have access to our confidential information. Our third-party collaborators also have access to large amounts of confidential information relating to our operations, including our research and development efforts. The size and complexity of our information technology systems, and those of third-party vendors and collaborators, and the large amounts of confidential information stored on those systems, make such systems potentially vulnerable to service interruptions or systems failures, or to security breaches from inadvertent or intentional actions by our employees, third-party vendors, and/or business partners, or from cyber-attacks by malicious third parties. In addition to such risks, the adoption of new technologies may also increase our exposure to cybersecurity breaches and failures. Cyber-attacks are increasing in their frequency, sophistication, and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, denial-of-service attacks, social engineering, "phishing" scams and other means to affect service reliability and threaten the confidentiality, integrity, and availability of information. Significant disruptions of these information technology systems or security breaches could adversely affect our business operations and/or result in the loss, misappropriation, and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including but not limited to trade secrets or other intellectual property, proprietary business information, and personal information), and could result in financial, legal, business, and reputational harm to us and would adversely affect our operations, including our discovery and research and development programs. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our employees of future clinical trial participants, could harm our reputation, require us to comply with federal and/or state breach notification laws and foreign law equivalents, and otherwise subject us to liability, including financial penalties and fines, under laws and regulations that protect

the privacy and security of personal information. Also, the loss of preclinical or clinical trial data from completed or future preclinical or clinical trials, respectively, could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, there is no assurance that such measures will prevent service interruptions or security breaches that could adversely affect our business.

Interruptions in the availability of server systems or communications with internet or cloud-based services, or failure to maintain the security, confidentiality, accessibility or integrity of data stored on such systems, could harm our business.

We rely upon a variety of internet service providers, third-party web hosting facilities and cloud computing platform providers to support our business. Failure to maintain the security, confidentiality, accessibility or integrity of data stored on such systems could result in interruptions in our operations, damage our reputation in the market, increase our service costs, cause us to incur substantial costs, subject us to liability for damages and/or fines, and divert our resources from other tasks, any one of which could materially adversely affect our business, financial condition, results of operations and prospects. If our security measures or those of our third-party data center hosting facilities, cloud computing platform providers, or third-party service partners, are breached, and unauthorized access is obtained to our data or our information technology systems, we may incur significant legal and financial exposure and liabilities.

We also do not have control over the operations of the facilities of our cloud service providers and our third party web hosting providers, and they also may be vulnerable to damage or interruption from natural disasters, cybersecurity attacks, terrorist attacks, power outages and similar events or acts of misconduct. In addition, any changes in these providers' service levels may adversely affect our ability to meet our requirements and operate our business

Legal, political and economic uncertainty surrounding the planned exit of the United Kingdom from the European Union is a source of instability and uncertainty.

In June 2016, a majority of the eligible members of the electorate in the United Kingdom voted to withdraw from the EU in a national referendum, commonly referred to as "Brexit." Subsequently, the United Kingdom and the EU agreed to a withdrawal agreement (the "Withdrawal Agreement"). The Withdrawal Agreement was approved by the United Kingdom Parliament and the United Kingdom formally left the EU on January 31, 2020. Under the Withdrawal Agreement, the United Kingdom is subject to a transition period until December 31, 2020 (the "Transition Period"), during which EU rules will continue to apply. Negotiations between the United Kingdom and the EU are expected to continue in relation to the customs and trading relationship between the United Kingdom and the EU following the expiry of the Transition Period.

The uncertainty concerning the United Kingdom's legal, political and economic relationship with the EU after the Transition Period may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise).

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime that applies to drugs and the approval of drug candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom. Given the lack of comparable precedent, it is unclear what financial, trade and legal implications the withdrawal of the United Kingdom from the EU, especially in the case of the United Kingdom leaving the EU without an agreement defining their respective trading rights and obligations, would have and how such withdrawal would affect us. The long-term impact of Brexit, including on our business and our industry, will depend on the terms that are negotiated in relation to the United Kingdom's future relationship with the EU, and we are closely monitoring the Brexit developments in order to determine, quantify and proactively address changes as they become clear.

Risks Related to Our Financial Position and need for Additional Capital

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;
- developing a sustainable and scalable manufacturing process for product candidates, including establishing and maintaining commercially viable supply relationships with third parties, such as CMOs, 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.

Our limited operating history may make difficult the evaluation of our business's success to date and assessment of our future viability.

We are a preclinical-stage company. We were founded and commenced operations in mid-2014. Our operations to date have been limited to organizing and staffing our company, business and scientific planning, raising capital, acquiring and developing technology, identifying potential product candidates, undertaking research and early preclinical studies of potential product candidates for ourselves and collaborators, developing the necessary manufacturing capabilities and evaluating a clinical path for our pipeline programs. All of our product candidates are still in the preclinical development stage. We have not yet demonstrated our ability to successfully initiate any clinical trials, including large-scale, pivotal clinical trials, obtain marketing approvals, manufacture clinical and commercial scale therapeutics, or arrange for a third-party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. 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 eventual commercialization of our product candidates, which may never occur. We may never be able to develop or commercialize a marketable product.

Each of our programs may require additional discovery research and then preclinical and clinical development, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, capacity and expertise, building of a commercial organization, substantial investment and significant marketing efforts before we generate any revenue from product sales. In addition, our product candidates must be approved for marketing by the FDA or certain other foreign regulatory agencies, including the EMA, before we may commercialize any product.

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

We have incurred net losses in each period since our inception, anticipate that we will continue to incur net losses in the future and may never achieve profitability.

We are not profitable and have incurred losses in each period since our inception. Our net loss was $99.5 million for the year ended December 31, 2019. As December 31, 2019, we had an accumulated deficit of $300.9 million. We expect these losses to increase as we continue to incur significant research and development and other expenses related to our ongoing operations, seek regulatory approvals for our future product candidates, scale-up manufacturing capabilities, maintain, expand and protect our intellectual property portfolio and hire additional personnel to support the development of our product candidates and to enhance our operational, financial and information management systems.

A critical aspect of our strategy is to invest significantly in our technology to improve the efficacy and safety of potential product candidates that we discover. Even if we succeed in discovering, developing and ultimately commercializing one or more of these product candidates, we will continue to incur losses for the foreseeable future relating to our substantial research and development expenditures to develop our technologies. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital. Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

We may need to raise substantial additional funding to fund our operations. If we fail to obtain additional financing, we may be unable to complete the development and commercialization of any product candidates.

Our operations have required substantial amounts of cash since inception, and we expect to spend substantial amounts of our financial resources on our discovery programs going forward and future development efforts. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development, manufacture (or have manufactured) product candidates and components, and then conduct extensive clinical trials to demonstrate the safety and efficacy of any of our future product candidates in humans. Because preclinical and clinical testing is expensive and can take many years to complete, we may require additional funding to complete these undertakings. Further, if we are able to identify product candidates that are eventually approved, we will require significant additional amounts in order to launch and commercialize our product candidates. For the foreseeable future, we expect to continue to rely on additional financing to achieve our business objectives.

We will require additional capital for the further development and commercialization of any product candidates and may need to raise additional funds sooner if we choose to expand more rapidly than we presently anticipate or due to other unanticipated factors.

We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development, manufacture or commercialization of our product candidates or other research and development initiatives. Our collaboration and license agreements may also be terminated if we are unable to meet the payment or other obligations under the agreements. We could be required to seek collaborators for product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to product candidates in markets where we otherwise would seek to pursue development or commercialization ourselves.

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

Raising additional capital may cause dilution to our stockholders and restrict our operations.

We will need additional capital in the future to continue our planned operations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing stockholders may be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

Our results of operations could be adversely affected by general conditions in the national or global economy and financial markets. For example, governmental statements, actions or policies, political unrest and global financial crises can cause extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, political unrest or additional global financial crises could result in a variety of risks to our business, including weakened demand for our products, if approved, or our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate, further political developments and financial market conditions could adversely impact our business.

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

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

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Risks Related to Our Reliance on Third Parties

Our technological advancements and any potential for revenue may be derived in part from our collaborations with Novartis and Regeneron, and if either of these collaboration agreements were to be terminated or materially altered, our business, financial condition, results of operations and prospects would be harmed.

In December 2014, we entered into a collaboration agreement with Novartis Institutes for BioMedical Research, Inc. ("Novartis"), as amended (the "2014 Novartis Agreement") regarding the discovery of new CRISPR/Cas9-based therapies principally using chimeric antigen receptor T ("CAR-T") cells and hematopoietic stem cells ("HSCs"). Under the Novartis collaboration agreement, we received a commitment to advance multiple programs. Pursuant to the 2014 Novartis Agreement, we granted Novartis exclusive rights to further develop and commercialize products arising out of the CAR-T cell program during the research term. Regarding HSCs, we are jointly advancing multiple programs with Novartis and have agreed to a process for assigning development and ownership rights, which may enable us to develop our own proprietary HSC pipeline. In December 2018, we expanded our collaboration agreement with Novartis to include discovery of CRISPR/Cas9-based therapies using certain limbal stem cells primarily against selected gene targets by Novartis. The research portion of our agreement with Novartis ended in December 2019, and we cannot guarantee that Novartis will continue to pursue programs that it has selected through our collaboration.

In April 2016, we entered into a collaboration agreement with Regeneron Pharmaceuticals, Inc. ("Regeneron") that includes a product component to research, develop and commercialize CRISPR/Cas-based therapeutic products primarily focused on genome 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/Cas9 technology to enhance our genome editing platform. Pursuant to the Regeneron collaboration agreement, we granted Regeneron exclusive rights to select up to 10 targets, subject to certain restrictions. We retained the rights to solely develop certain indications, other than ATTR, which is subject to a Co/Co agreement with Regeneron. We also have the right to choose additional liver targets for our own development during the collaboration term, which may be subject to additional Co/Co options by Regeneron. In July 2018, we entered into the first Co/Co agreement directed to ATTR (the "ATTR Co/Co"), under which we will be the clinical and commercial lead for ATTR activities. On December 13, 2019, Regeneron informed us that it would exercise its right under the ATTR Co/Co agreement to modify its shares of worldwide developments costs and profits from 50% to 25%, effective six months after its notice. Pursuant to the ATTR Co/Co agreement, Regeneron funded approximately 50% of the program's development costs through 2019. Starting June 2020 and thereafter, Regeneron will share approximately 25% of worldwide development costs and commercial profits for the ATTR program. We continue to lead the development and commercialization of any resulting ATTR products.

Either Novartis or Regeneron may change its strategic focus or pursue alternative technologies in a manner that results in reduced, delayed or no revenue to us. Each of Novartis and Regeneron has a variety of marketed products and product candidates either by itself or under collaboration with other companies, including some of our competitors, and the respective corporate objectives of Novartis or Regeneron may not be consistent with our best interests. Regeneron may change its position regarding its participation and funding of our joint ATTR activities, which may impact our ability to successfully pursue that program. If either of our collaboration partners fails to develop, obtain regulatory approval for or ultimately commercialize any product candidate from the development programs governed by the respective collaboration agreement in the applicable territories, or if either of our collaboration partners breaches or terminates our collaboration with it, our business, financial condition, results of operations and prospects could be harmed. In addition, any material alteration of the collaboration agreements, or dispute or litigation proceedings we may have with either Novartis or Regeneron in the future could delay development programs, create uncertainty as to ownership of or access to intellectual property rights, distract management from other business activities and generate substantial expense.

Our existing and future collaborations will be important to our business. If we are unable to maintain any of these collaborations, or if these collaborations are not successful, our business could be adversely affected.

We have limited capabilities for product discovery and development and do not yet have any capability for sales, marketing or distribution. Accordingly, we have entered, and plan to enter, into collaborations with other companies, including our therapeutic-focused collaboration agreements with Novartis and Regeneron, that we believe can provide such capabilities. These therapeutic-focused collaborations provide us with important technologies and/or funding for our programs and technology, and we expect to receive additional technologies and funding under these and other collaborations in the future. Our existing therapeutic collaborations, and any future collaborations we enter into, may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply;
- collaborators may not perform their obligations as expected;
- collaborators may dispute the amounts of payments owed;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs or license arrangements based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as a strategic transaction that may divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

- collaborators could develop independently, or with third parties, products that compete directly or indirectly with our products and product candidates if the collaborators believe that the competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the development or commercialization of our product candidates;
- collaborators may dispute ownership or rights in jointly developed technologies or intellectual property;
- collaborators may fail to comply with applicable legal and regulatory requirements regarding the development, manufacture, sale, distribution or marketing of a product candidate or product;
- collaborators with sales, marketing, manufacturing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the sale, marketing, manufacturing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation, payment obligations or the preferred course of discovery, development, sales or marketing, might cause delays or terminations of the research, development or commercialization of product candidates, might lead to additional and burdensome responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend their or our relevant intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation and liability;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;
- if a collaborator of ours is involved in a business combination or cessation, the collaborator might deemphasize or terminate the development or commercialization of any product candidate licensed to it by us; and
- collaborations may be terminated by the collaborator, and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates, or potentially lose access to the collaborator's intellectual property.

If our therapeutic collaborations do not result in the successful discovery, development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development and commercialization of our technology and product candidates could be delayed and we may need additional resources to develop product candidates and our technology. All of the risks relating to product discovery, development, regulatory approval and commercialization described in this report also apply to the activities of our therapeutic collaborators.

Additionally, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our perception in the business and financial communities could be adversely affected.

For some of our programs, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for discovery, development and potential commercialization of therapeutic products. We face significant competition in seeking appropriate collaborators because, for example, third-parties have comparable rights to the CRISPR/Cas9 system or similar genome editing technologies. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at

all, we may have to curtail discovery efforts or the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential manufacture or commercialization, or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake discovery, development, manufacturing or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary discovery, development, manufacturing and commercialization activities, we may not be able to further develop our product candidates, manufacture the product candidates, bring them to market or continue to develop our technology and our business may be materially and adversely affected.

We expect to rely in part on third parties to manufacture our clinical product supplies, and we intend to rely on third parties for at least a portion of the manufacturing process of our product candidates, if approved. Our business could be harmed if the third parties fail to provide us with sufficient quantities of product inputs or fail to do so at acceptable quality levels or prices or fail to meet legal and regulatory requirements.

We do not currently own any facility that may be used as our clinical-scale manufacturing and processing facility and must rely on outside vendors, such as CMOs, to manufacture supplies and process our product candidates. We have only recently begun to manufacture and process product candidate components on a clinical scale and may not be able to successfully complete or continue to do so for our product candidates. We will make changes as we work to optimize the manufacturing process, and we cannot be sure that even minor changes in the process will result in therapies that are safe, potent, pure or effective.

The facilities used by our contract manufacturers to manufacture our product candidates must be inspected and approved by the FDA or other foreign regulatory agencies pursuant to inspections that will be conducted after we submit an application to the FDA or other foreign regulatory agencies. We will be dependent on our contract manufacturing partners to manufacture adequate supply of our product candidates and components in a timely manner and in accordance with our specification. We also will depend on these entities for compliance with legal and regulatory requirements for manufacture, including current good manufacturing practice ("cGMP"), and in certain cases, current good tissue practice ("cGTP"), requirements of our product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel, particularly as we increase the scale of our manufactured material. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

We will rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or comply with legal and regulatory requirements, we may not be able to obtain regulatory approval of or commercialize any potential product candidates.

We will depend upon third parties, including independent investigators, to conduct our clinical trials under agreements with universities, medical institutions, CROs, strategic partners and others. We expect to have to negotiate budgets and contracts with CROs and trial sites, which may result in delays to our development timelines and increased costs.

We will rely heavily on third parties over the course of our clinical trials, and, as a result, will have limited control over the clinical investigators and limited visibility into their day-to-day activities, including with respect to their compliance with the approved clinical protocol and other legal, regulatory and scientific standards. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our legal responsibilities. We and these third parties are required to comply with good clinical practice ("GCP") requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of these third parties fail to comply

with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to suspend or terminate these trials or perform additional preclinical studies or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the GCP requirements. In addition, our clinical trials must be conducted with product produced under cGMP, and in certain cases, cGTP, requirements and may require a large number of test patients.

Our failure or any failure by these third parties to comply with these requirements or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates applicable federal, state or local, as well as foreign, laws and regulations, such as the fraud and abuse or false claims laws and regulations or privacy and security laws.

Any third parties conducting our future clinical trials will not be our employees and, except for remedies that may be available to us under our agreements with such third parties, we cannot control whether they devote sufficient time and resources to our ongoing preclinical, clinical, and nonclinical programs. These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could affect their performance on our behalf. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed.

If any of our relationships with these third-party CROs or others terminate, we may not be able to enter into arrangements with alternative CROs or other third parties or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, the transition to a new CRO may result in delays, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

Risks Related to Employee Matters and Managing Growth

We expect to expand our research, development, manufacturing, clinical and regulatory capabilities, and, as a result, we may encounter difficulties in hiring capable personnel and otherwise managing our growth, which could disrupt our operations.

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

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

We are highly dependent on the research and development, clinical, legal, financial and business development expertise of John M. Leonard, M.D., our President and Chief Executive Officer, Glenn Goddard, our Executive Vice President and Chief Financial Officer, José E. Rivera, our Executive Vice President, General Counsel, Andrew Schiermeier, our Executive Vice President and Chief Operating Officer and Laura Sepp-Lorenzino, our Executive Vice President and Chief Scientific Officer as well as the other principal members of our management, scientific and clinical teams. Although we have entered into employment arrangements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be important for our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products using our technology. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies, universities and research institutions for similar personnel. The market for qualified personnel in the biotechnology space generally, and genome editing and gene therapy fields in particular, in and around the Cambridge, Massachusetts area is especially competitive. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategies. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. Further, some of the qualified personnel that we hire and recruit are not U.S. citizens, and there is uncertainty with regard to their future employment status due to the current U.S. administration's announced intention of modifying the legal framework for non-U.S. citizens to be employed in the U.S. If we are unable to continue to attract and retain high quality personnel, our ability to pursue our growth strategy will be limited.

Risks Related to Government Regulation

While the regulatory framework for approval of gene therapy including genome editing products exists, the lack of specific guidance and precedent for genome-edited products makes the regulatory approval process potentially more unpredictable and we may experience significant delays in the clinical development and regulatory approval, if any, of our product candidates.

The research, testing, manufacturing, labeling, approval, selling, import, export, marketing and distribution of drug products, including genome editing therapeutics and engineered cell therapies, are subject to extensive regulation by the FDA in the U.S. and other regulatory authorities. We are not permitted to market any drug or biological product, including *in vivo* products or engineered cell therapies, in the U.S. until we receive regulatory approval from the FDA. We have not previously submitted a BLA to the FDA, or similar approval filings to comparable foreign authorities. A BLA must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe and effective or, for biological products, safe, pure and potent for each desired indication. The application must also include significant information regarding the chemistry, manufacturing and controls for the product, and the manufacturing facilities must complete a successful pre-approval inspection by the FDA, or applicable foreign authority, prior to the approval or licensure of the product. We expect the novel nature of our product candidates to create further challenges in obtaining regulatory approval. For example, the FDA has not approved any nuclease edited cell therapies for human therapeutic use. The FDA may also require a panel of experts, referred to as an Advisory Committee, to deliberate on the adequacy of the safety and efficacy data to support approval. The opinion of the Advisory Committee, although not binding, may have a significant impact on our ability to obtain approval of any product candidates that we develop based on the completed clinical trials. Moreover, while we are not aware of any specific genetic or biomarker diagnostic tests for which regulatory approval would be necessary in order to advance any of our product candidates to clinical trials or potential commercialization, in the future regulatory agencies may require the development and approval of such tests. Accordingly, the regulatory approval pathway for such product candidates may be uncertain, complex, expensive and lengthy, and approval may not be obtained.

In December 2018, the World Health Organization ("WHO") established the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. While the standards are expected to focus primarily on germline modifications, the guidelines could impact somatic cell editing research programs.

In August 2019, the WHO Expert Advisory Committee recommended initiating the first phase of a new global registry to track research on human genome editing. Accepting this recommendation, the WHO announced plans for an initial phase of the registry using the International Clinical Trials Registry Platform ("ICTRP"). This phase will include worldwide registries for both somatic cell editing and germline editing clinical trials. Registration of these clinical trials in the WHO's registry is voluntary.

In addition, clinical trials can be delayed or terminated for a variety of reasons, including delays or failures related to:

- obtaining and maintaining regulatory authorization to conduct a trial, if applicable;
- the availability of financial resources to begin and complete the planned trials;
- reaching agreement on acceptable terms with prospective CROs, clinical trial sites and clinical investigators, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining approval at each clinical trial site by an independent IRB;
- recruiting suitable patients to participate in a trial in a timely manner;
- having patients complete a trial or return for post-treatment follow-up;
- clinical trial sites deviating from trial protocol, not complying with GCP requirements or dropping out of a trial;
- addressing any patient safety concerns that arise during the course of a trial;
- addressing any conflicts with new or existing laws or regulations;
- adding new clinical trial sites; or
- manufacturing qualified materials under cGMP regulations for use in clinical trials.

Patient enrollment is a significant factor in the timing of clinical trials and is affected by many factors. Further, a clinical trial may be suspended or terminated by us, the IRBs for the institutions in which such trials are being conducted, the DSMB for such trial or the FDA or other regulatory authorities 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 the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience termination of, or delays in the completion of, any clinical trial of product candidates, the commercial prospects for our product candidates will be harmed, and our ability to generate product revenue will be impaired. In addition, any delays in completing any clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenue.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also authorize the manufacturing, marketing and sale of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the U.S., including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the U.S., a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we are allowed to charge for our products is also subject to approval.

Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets or to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Even if we receive regulatory approval of any product candidates or therapies, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

If any of our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, distribution, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies and submission of safety and efficacy data, and other post-market information, including both federal and state requirements in the U.S. and requirements of comparable foreign regulatory authorities. In addition, we will be subject to continued compliance with cGMP and GCP, and in certain cases, cGTP, requirements for any clinical trials that we conduct post-approval.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA and comparable foreign regulatory authority requirements, including ensuring that quality control and manufacturing procedures conform to cGMP and, in certain cases, cGTP requirements. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA, other marketing applications, and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, we will have to comply with legal or regulatory requirements including submissions of safety and other post-marketing information and reports and registration.

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

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

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the U.S. market. Products may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

The policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the U.S. or abroad. For example, certain policies of the current or future U.S. administration may impact our business and industry. Namely, the current administration has taken, or may take, several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking and issuance of guidance. It is difficult to predict how any of these rules or requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory and legal compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

Healthcare cost control initiatives, including healthcare legislative and regulatory reform measures, may have a material adverse effect on our business and results of operations.

The U.S. and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates or any future product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) additional regulation or restrictions on pricing and reimbursement; (iv) changes to private or governmental insurance practices; (v) the recall or discontinuation of our products; or (vi) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In both the U.S. and certain foreign jurisdictions, there have been, and are expected to continue to be, a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In the U.S., however, significant uncertainty exists regarding the provision and financing of health care because the current administration and federal legislators have publicly declared their intention to significantly modify the current legal and regulatory framework for the health care system but details have not been agreed upon or disclosed.

Current legislation at the U.S. federal and state levels seeks to reduce healthcare costs and improve the quality of healthcare. In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the "Affordable Care Act", or "ACA"), was enacted, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacted the U.S. pharmaceutical and biotechnology industry. The Affordable Care Act, among other things, subjects biologic products to potential competition by lower-cost biosimilars, addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increases the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extends the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjects manufacturers to new annual fees and taxes for certain branded prescription drugs and biologic agents, creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D, and provides incentives to programs that increase the federal government's comparative effectiveness research. At this time, the full effect that the Affordable Care Act would have on our business remains unclear.

Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as recent efforts by the current administration to repeal or replace certain aspects of the Affordable Care Act. Since January 2017, the U.S. president has signed two executive orders and other directives designed to delay the implementation of certain provisions of the Affordable Care Act. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the Affordable Care Act. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the Affordable Care Act. Further, significant uncertainty exists regarding the future scope and effect of the Affordable Care Act because the current administration and federal legislators have publicly declared their intention to significantly modify or repeal the legislation, and there are conflicting judicial decisions regarding the constitutionality of the law which at least one federal court has ruled is unconstitutional. We cannot predict the ultimate form or timing of any modification to, or repeal of, the Affordable Care Act or the effect that such modification or repeal would have on our business. Public announcements by the U.S. administration and members of the U.S. Congress have emphasized the administration's significant interest in pursuing healthcare reform. Such reform efforts and any resulting changes to the Affordable Care Act, or related regulations and laws, could impact our ability to sell our products profitably.

Other legislative changes relevant to the health care system have been adopted in the U.S. since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and, due to subsequent legislative amendments, will remain in effect through 2029 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers, cancer centers and other treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In December 2017, the U.S. president signed into law the Tax Cuts and Jobs Act ("TCJA") which, among other things, repealed the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year (the "individual mandate"), effective January 1, 2019. On December 14, 2018, a U.S. District Court

Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and therefore, because it was repealed as part of the TCJA, the remaining provisions of the Affordable Care Act are invalid as well. The current Administration and CMS have both stated that the ruling will have no immediate effect, and on December 18, 2019, the Fifth Circuit U.S. Court of Appeals held that the individual mandate is unconstitutional, and remanded the case to the lower court to reconsider its earlier invalidation of the full Affordable Care Act. The State of California and the other plaintiffs in this case have asked the U.S. Supreme Court for authorization to appeal the decision of the Fifth Circuit. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. We will continue to evaluate the effect that the ACA and its possible repeal and replacement has on our business. These laws may result in additional reductions in Medicare, Medicaid and other healthcare funding, or insured patients generally, which could have a material adverse effect on our future, potential customers and, accordingly, our financial operations.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. As indicated previously, significant uncertainty exists regarding the future scope and effect of current health care legislation and regulations because the current administration and federal legislators have publicly declared their intention to significantly modify or repeal the current legislative framework. We cannot predict the initiatives that may be adopted in the future, any of which could limit or modify the amounts that foreign, federal and state governments as well as private payors, including patients, will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

The continuing efforts of governments, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls could harm our business, financial conditions and prospects and may adversely affect:

- the demand for or utilization of our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes, fees and rebates that we are required to pay; and
- the availability of capital.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, lower reimbursement, and new payment methodologies. This could lower the price that we receive for any approved product. Any denial in coverage or reduction in reimbursement from Medicare or other government-funded programs may result in a similar denial or reduction in payments from private payors, which may prevent us from being able to generate sufficient revenue, attain profitability or commercialize our product candidates, if approved.

Our employees, independent contractors, clinical investigators, CMOs, CROs, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of non-compliance, fraud, misconduct or other illegal activity by our employees, independent contractors, clinical investigators, CMOs, CROs, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and/or negligent conduct that fails to: comply with federal and state laws and those of other applicable jurisdictions; provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies; comply with manufacturing standards; comply with federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the U.S. and similar foreign privacy or fraudulent misconduct laws; or report financial information or data accurately; or disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the U.S., our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with clinical investigators and research patients, as well as proposed and future sales, marketing and education programs. In particular, the promotion, sales and marketing of healthcare products and services, as well as

certain business arrangements in the healthcare industry, are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, including promotion and marketing of off-label uses of our products, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws, health information privacy and security laws and anti-corruption laws. If we are unable to comply, or have not fully complied, with such laws or their relevant foreign counterparts, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the U.S., our operations may be directly, or indirectly through our future, potential customers and third-party payors, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act ("FCA"), and data privacy and physician sunshine laws and regulations. These laws or their relevant foreign counterparts may impact, among other things, our proposed sales, marketing, and education programs and our relationships with healthcare providers, physicians and other parties through which we market, sell and distribute our products for which we obtain marketing approval. In addition, we may be subject to patient privacy regulation by the federal government and the states in the U.S. as well as other jurisdictions. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, individuals or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or certain rebates), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement for or recommendation of the purchase, lease, order, arrangement for any good, facility, item or service, for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal FCA. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. Violators are subject to civil and criminal fines and penalties, as well as imprisonment and exclusion from government healthcare programs;

- federal civil and criminal false claims laws, including, without limitation, the federal FCA, and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from the federal government, including Medicare, Medicaid and other government payors, that are false or fraudulent or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or to avoid, decrease or conceal an obligation to pay money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims by, for example, promoting a product off-label. The FCA also permits a private individual acting as a "whistleblower" to bring civil whistleblower or *qui tam* actions against individuals (including biopharmaceutical manufacturers and sellers) on behalf of the federal government alleging violations of the FCA and to share in any monetary recovery. These laws impose criminal and civil penalties on violators;

- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and its implementing regulations, which impose criminal and civil liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. HIPAA violations can lead to civil and criminal liability;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH"), and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, 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 attorneys' fees and costs associated with pursuing federal civil actions. In addition, state and non-U.S. laws govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effective requirements, thus complicating compliance efforts to comply with their respective provisions;
- the U.S. federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act," created under the Affordable Care Act, and their implementing regulations, which require manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare providers, and teaching hospitals, as well as ownership and investment interests held by physicians, other healthcare providers, and their immediate family members. Failure to submit required information may result in civil monetary penalties for all payments, transfers of value or ownership or investment interests that are not timely, accurately, and completely reported in an annual submission. Effective January 1, 2022, the U.S. federal physician transparency reporting requirements will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- the Foreign Corrupt Practices Act ("FCPA") and other laws which prohibit improper payments or offers of payments to foreign governments and their officials and political parties by U.S. persons and issuers as defined by the statute for the purpose of obtaining or retaining business;
- the Federal Food, Drug and Cosmetic Act, which prohibits, among other things, the commercialization of adulterated or misbranded drugs and medical devices and the Public Health Service Act, which prohibits, among other things, the commercialization of biological products unless a biologics license is in effect; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and may be broader in scope than their federal equivalents; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

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

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

As of May 25, 2018, the General Data Protection Regulation ("GDPR") regulates the collection and use of personal data in the EU. The GDPR covers any business, regardless of its location, that provides goods or services to residents in the EU and, thus, could incorporate our activities in EU member states. The GDPR imposes strict requirements on controllers and processors of personal data, including special protections for "sensitive information," which includes health and genetic information of individuals residing in the EU. GDPR grants individuals the opportunity to object to the processing of their personal information, allows them to request deletion of personal information in certain circumstances, and provides the individual with an express right to seek legal remedies in the event the individual believes his or her rights have been violated. Further, the GDPR imposes strict rules on the transfer of personal data out of the EU to regions that have not been deemed to offer "adequate" privacy protections, such as the U.S. currently. Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU member states, which may deviate slightly from the GDPR, may result in warning letters, mandatory audits and financial penalties, including fines of up to 4% of global revenues, or 20,000,000 Euro, whichever is greater. As a result of the implementation of the GDPR, we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules.

There is significant uncertainty related to the manner in which data protection authorities will seek to enforce compliance with GDPR. For example, it is unclear whether the authorities will conduct random audits of companies doing business in the EU, or act solely after complaints are filed claiming a violation of the GDPR. The lack of compliance standards and precedent, enforcement uncertainty and the costs associated with ensuring GDPR compliance may be onerous and adversely affect our business, financial condition, results of operations and prospects. Further, the United Kingdom's exit from the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. In particular, it is unclear how data transfers to and from the United Kingdom will be regulated, and what other aspects of EU privacy laws will be adopted, rejected or modified by the United Kingdom.

California recently enacted the California Consumer Privacy Act ("CCPA"), which creates new individual privacy rights for California consumers (as defined in the law) and places increased privacy and security obligations on entities handling personal data of consumers or households. The CCPA will require covered companies to provide certain disclosures to consumers about its data collection, use and sharing practices, and to provide affected California residents with ways to opt-out of certain sales or transfers of personal information. The CCPA went into effect on January 1, 2020, and the California Attorney General will commence enforcement actions against violators beginning July 1, 2020. As currently written, the CCPA may impact our business activities. The California Attorney General has proposed draft regulations, which have not been finalized to date, that may further impact our business activities if they are adopted. The uncertainty surrounding the implementation of CCPA exemplifies the vulnerability of our business to the evolving regulatory environment related to personal data and protected health information.

The increasingly global nature of our business operations subjects us to domestic and foreign anti-bribery and anti-corruption laws and regulations, such as the FCPA. Activities conducted in jurisdictions outside of the U.S. create the risk of unauthorized payments or offers of payments that are prohibited under the FCPA or comparable laws and regulations. It is our policy to implement safeguards to discourage these practices by our employees. However, these safeguards may ultimately prove ineffective, and our employees, consultants, and agents may engage in conduct for which we might be held responsible. Violations of the FCPA may result in severe criminal or civil sanctions, and we may be subject to other liabilities, which could negatively affect our business, operating results and financial condition.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations as well as other domestic and foreign legal requirements will involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, disgorgement, monetary fines, individual imprisonment, possible exclusion from participation in Medicare, Medicaid and other U.S. federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our results of operations. Any action for violation of these laws, even if successfully defended, could cause a pharmaceutical manufacturer to incur significant legal expenses and divert management's attention from the operation of the business. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, that person or entity may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Prohibitions or restrictions on sales or withdrawal of future marketed products could materially affect business in an adverse way. In addition, the approval and commercialization of any of our product candidates outside the U.S. will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

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

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

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

In the event we conduct clinical trials in the European Economic Area ("EEA"), we may be subject to additional privacy laws. The GDPR became effective on May 25, 2018 and deals with the processing of personal data and on the free movement of such data. The GDPR imposes a broad range of strict requirements on companies subject to the GDPR, including requirements relating to having legal bases for processing personal information relating to identifiable individuals and transferring such information outside the EEA, including to the U.S., providing details to those individuals regarding the processing of their personal information, keeping personal information secure, having data processing agreements with third parties who process personal information, responding to individuals' requests to exercise their rights in respect of their personal information, reporting security breaches involving personal data to the competent national data protection authority and affected individuals, appointing data protection officers, conducting data protection impact assessments, and record-keeping. The GDPR increases substantially the penalties to which we could be subject in the event of any non-compliance, including fines of up to 10,000,000 Euros or up to 2% of our total worldwide annual turnover for certain comparatively minor offenses, or up to 20,000,000 Euros or up to 4% of our total worldwide annual turnover for more serious offenses. Given the new law, we face uncertainty as to the exact interpretation of the new requirements and we may be unsuccessful in implementing all measures required by data protection authorities or courts in interpretation of the new law.

In particular, national laws of member states of the EU are in the process of being adapted to the requirements under the GDPR, thereby implementing national laws which may partially deviate from the GDPR and impose different obligations from country to country, so that we do not expect to operate in a uniform legal landscape in the EU. Also, as it relates to processing and transfer of genetic data, the GDPR specifically allows national laws to impose additional and more specific requirements or restrictions, and European laws have historically differed quite substantially in this field, leading to additional uncertainty.

In the event we conduct clinical trials in the EEA, we must also ensure that we maintain adequate safeguards to enable the transfer of personal data outside of the EEA, in particular to the U.S., in compliance with European data protection laws. We expect that we will continue to face uncertainty as to whether our efforts to comply with our obligations under European privacy laws will be sufficient. If we are investigated by a European data protection authority, we may face fines and other penalties. Any such investigation or charges by European data protection authorities could have a negative effect on our existing business and on our ability to attract and retain new clients or pharmaceutical partners. We may also experience hesitancy, reluctance, or refusal by European or multi-national clients or pharmaceutical partners to continue to use our products and solutions due to the potential risk exposure as a result of the current (and, in particular, future) data protection obligations imposed on them by certain data protection authorities in interpretation of current law, including the GDPR. Such clients or pharmaceutical partners may also view any alternative approaches to compliance as being too costly, too burdensome, too legally uncertain, or otherwise objectionable and therefore decide not to do business with us. Any of the foregoing could materially harm our business, prospects, financial condition and results of operations.

If we fail to comply with environmental, health and safety, and laboratory animal welfare laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous federal, state and local environmental, health and safety, and laboratory animal welfare laws and regulations. These legal requirements include those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes as well as those which regulate the care and use of animals in research. Our operations will involve research using research animals and the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also may produce hazardous waste products. We generally anticipate contracting with third parties for the disposal of these materials and wastes. We will not be able to eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from any use by us of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety, and laboratory animal welfare laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Failure to comply with labor and employment laws and regulations could subject us to legal liability and costs, including fines or penalties, as well as reputational damage that could harm our business.

We are subject to numerous federal, state and local laws and regulations relating to the recruiting, hiring, compensation and treatment of employees and contractors. These laws and regulations cover financial compensation (including wage and hour standards), benefits (including insurance and 401K plans), discrimination, workplace safety and health, benefits, and workers' compensation. In varying degrees and scope, national, state and local laws prohibit unfavorable or unfair treatment in the workplace of employees or candidates based on their age, gender, race, national origin, religion, disability or sexual orientation. Disability laws also expand upon the employment rights of veterans and persons with disabilities. At a federal level, Title VII of the Civil Rights Act of 1964 prohibit discrimination on the basis of race, color, religion, sex or national origin. The Fair Labor Standards Act establishes a national minimum wage, guarantees "time-and-a-half" for overtime in certain jobs, and prohibits oppressive employment of minors. The Americans with Disabilities Act, as amended, prohibits discrimination based on disability.

The Commonwealth of Massachusetts also has laws that expand on these federal laws or create additional rights for employees or obligations for employers. For example, on July 1, 2018, the Massachusetts Equal Pay Act went into effect, which added protections employers must comply with regarding pay equity for "comparable work". There is currently uncertainty regarding the exact scope of these new legal limits and such uncertainty may remain for the foreseeable future. We may face increased employment and legal costs to ensure we are complying with this law. In addition, on October 1, 2018, a new Massachusetts non-compete law went into effect, placing additional restrictions on employers seeking to enter into non-competition agreements with employees. This law may negatively impact our ability to prevent employees from working with direct or indirect competitors in the future and may affect our ability to retain key talent in a competitive market.

Our failure to comply with these and other related laws could expose us to civil and, in some cases, criminal liability, including fines and penalties. Further, government or employee claims that we have violated any of these laws, even if ultimately disproven, could result in increased expense and management distraction, as well as have an adverse reputational impact on us.

Risks Related to Our Intellectual Property

Third-party claims of intellectual property infringement against us, our licensors or our collaborators may prevent or delay our product discovery and development efforts.

Our commercial success depends in part on our avoiding infringement of the valid patents and proprietary rights of third parties.

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our product candidates. As industry, government, academia and other biotechnology and pharmaceutical research expands and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others. We cannot guarantee that our technology, future product candidates or the use of such product candidates do not infringe third-party patents. It is also possible that we have failed to identify relevant third-party patents or applications. Because patent rights are granted jurisdiction-by-jurisdiction, our freedom to practice certain technologies, including our ability to research, develop and commercialize our product candidates, may differ by country.

Third parties may assert that we infringe their patents or that we are otherwise employing their proprietary technology without authorization, and may sue us. There may be third-party patents of which we are currently unaware with claims to compositions, formulations, methods of manufacture or methods of use or treatment that cover product candidates we discover and develop. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies or the manufacture, use or sale of our product candidates infringes upon these patents. If any such third-party patents were held by a court of competent jurisdiction to cover our technologies or product candidates, the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business.

Third parties may seek to claim intellectual property rights that encompass or overlap with intellectual property that we own or license from them or others. Legal proceedings may be initiated to determine the scope and ownership of these rights, and could result in our loss of rights, including injunctions or other equitable relief that could effectively block our ability to further develop and commercialize our product candidates. For example, through the Caribou License, we sublicense the rights of the Regents of the University of California and the University of Vienna (collectively, "UC/Vienna") to a worldwide patent portfolio that 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 eukaryotic cells. We sublicense the UC/Vienna rights to this portfolio for human therapeutic, prophylactic and palliative uses, including companion diagnostics, except for anti-fungal and anti-microbial uses. This patent portfolio to-date includes, for example, multiple granted, allowed, and/or allowable patent applications in the U.S., as well as granted patents from the European Patent Office, the United Kingdom's Intellectual Property Office, the German Patent and Trade Mark Office, Australia's Intellectual Property agency and China's Intellectual Property Office, among others. Because UC/Vienna co-own this portfolio with Dr. Emmanuelle Charpentier (from whom we do not have sublicense rights), we refer to this co-owned worldwide patent portfolio as the UC/Vienna/Charpentier patent family. UC/Vienna could challenge Caribou's rights under their license agreement, including Caribou's right to sublicense its rights to others, such as Intellia, and on what terms such a sublicense would be granted, each of which could adversely impact our rights under our license agreement with Caribou.

Similarly, on October 17, 2018, we initiated an arbitration proceeding with JAMS against Caribou asserting that Caribou is violating the terms and conditions of the Caribou License, as well as other contractual and legal rights, by using and seeking to license to third parties technology covered by two patent families (described in, for instance, PCT No. PCT/US2016/015145 and PCT No. PCT/US2016/064860, and related patents and applications) relating to specific structural or chemical modifications of guide RNAs, that were purportedly invented or controlled by Caribou, in our exclusive human therapeutic field. Caribou asserted that the two families of IP are outside the scope of our field of use under the license rights granted to us under the Caribou License.

On September 26, 2019, we announced that the arbitration panel issued an interim award concluding that both the structural and chemical guide RNAs modification technologies were exclusively licensed to us by Caribou pursuant to the Caribou License. After concluding that the chemical modification technology was within the scope of our exclusive license from Caribou, the arbitration panel nevertheless noted that its decision could delay or otherwise adversely impact the development of these modified guide RNAs as human therapeutics. It also noted that we currently are not using these modified guide RNAs in any of our active programs. Thus, solely with respect to the particular modified guide RNAs, the arbitration panel stated that it will declare that Caribou has an equitable "leaseback," which it described as exclusive, perpetual and worldwide (the "Caribou Award"). The panel instructed the parties to negotiate the terms of the Caribou Award, including Caribou's future payments to us for the same, but the parties' negotiations reached an impasse.

On February 6, 2020, after considering additional submissions from the parties, the panel clarified that the Caribou Award is limited to a particular on-going Caribou program, which seeks to develop a CAR-T cell product directed at CD19. The panel instructed the parties to seek to negotiate terms based on this scope. Accordingly, the Caribou Award will be subject to terms, including Caribou's future payments to us to be negotiated by the parties or, if unsuccessful, adjudicated in additional arbitration or judicial proceedings.

Pursuant to the September 2019 interim award, the Caribou Award by the panel does not include the structural guide modifications intellectual property at issue in the arbitration, any other intellectual property exclusively licensed or sublicensed by Caribou to us under the Caribou License (including but not limited to the foundational CRISPR/Cas9 intellectual property co-owned by University of California, University of Vienna and Dr. Emmanuelle Charpentier), or any other of our intellectual property.

Upon, and subject to the terms of, a final award, which will follow further arbitration or legal proceedings, Caribou could be able to use the modified guide RNAs at issue for CAR-T cell human therapeutics directed at CD19. Either we or Caribou may challenge the arbitration panel's decisions under limited circumstances. The additional time and legal costs associated with negotiating or arbitrating the terms of the Caribou Award, as well as its final terms, could adversely impact our exclusive right to use the particular modified guide RNAs in dispute and enable Caribou's ability to compete with us (or our licensees) in the development of CAR-T cell human therapeutics directed at CD19, each of which may adversely affect our business.

In addition, third parties could assert that UC/Vienna/Charpentier do not have rights to the CRISPR/Cas9 technology, or that any rights owned by UC/Vienna/Charpentier are limited. For example, under our sublicense from Caribou, we have rights to patent applications owned by UC/Vienna Charpentier covering certain aspects of CRISPR/Cas9 systems to edit genes in eukaryotic cells, including human cells (collectively, the "UC/Vienna/Charpentier eukaryotic patent family"). The Broad Institute, Massachusetts Institute of Technology, the President and Fellows of Harvard College and the Rockefeller University (collectively, the "Broad Institute") co-own patents and patent applications that also claim CRISPR/Cas9 systems to edit genes in eukaryotic cells (collectively, the "Broad Institute patent family"). Because the respective owners of various UC/Vienna/Charpentier patent applications and the Broad Institute patent family both allege owning intellectual property claiming overlapping aspects of CRISPR/Cas9 systems and methods to edit genes in eukaryotic cells, including human cells, our ability to market and sell CRISPR/Cas9-based human therapeutics may be adversely impacted depending on the scope and actual ownership over the inventions claimed in the competing patent portfolios. On June 25, 2019, the Patent Trial and Appeal Board ("PTAB") of the U.S. Patent and Trademark Office ("USPTO") declared an interference between the UC/Vienna/Charpentier eukaryotic patent family and the Broad Institute patent family to determine which research group first invented the use of the CRISPR/Cas9 technology in eukaryotic cells and, therefore, is entitled to the patents covering the invention. On August 26, 2019, the PTAB redeclared the interference to include additional UC/Vienna/Charpentier patent applications covering the invention that had also been found allowable by the USPTO. If it were to succeed in the interference, the Broad could seek to assert its issued patents against us based on our CRISPR/Cas9-based activities, including commercialization. Defense of these claims, regardless of their merit, would involve substantial litigation expense, would be a substantial diversion of management and other employee resources from our business and may impact our reputation. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. In that event, we could be unable to further develop and commercialize our product candidates, which could harm our business significantly.

In addition, other third parties, such as Vilnius University, ToolGen, Inc., MilliporeSigma (a subsidiary of Merck KGaA) and Harvard University, filed patent applications claiming CRISPR/Cas9-related inventions around or within a year after the UC/Vienna/Charpentier application was filed and may allege that they invented one or more of the inventions claimed by UC/Vienna/Charpentier before UC/Vienna/Charpentier. If the USPTO deems the scope of the claims of one or more of these parties to sufficiently overlap with the allowable claims from the UC/Vienna/Charpentier application, the USPTO could declare other interference proceedings to determine the actual inventor of such claims. If these third-parties were to prevail in their inventorship claims or obtain patent claims that cover our product candidates or related activities through these various legal proceedings, then we could be prevented from developing and commercializing all or some of our products candidates unless we can obtain rights to the third-parties' intellectual property, or avoid or invalidate it.

Third parties could also assert patent rights against us to seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize product candidates. For example, the Broad Institute or other third-parties that own issued patents, including patents claiming aspects of the CRISPR-Cas9 technology, could seek to assert such patents against us claiming that our activities, including those relating to the CRISPR-Cas9 technology, infringe their respective patents. Defense of these or similar claims, regardless of their merit, would involve substantial legal expense, would be a substantial diversion of management and other employee resources from our business and may impact our reputation. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for any adjudicated willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. In that event, we may be unable to further develop and commercialize our product candidates, which could harm our business significantly.

Third parties asserting their patent rights against us may seek and obtain injunctive or other equitable relief, which could effectively limit or block our ability to further develop and commercialize our product candidates. If we are found to infringe a third-party's valid intellectual property rights, we could be required to obtain a license from such third-party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing, manufacturing or importing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing one or more of our product candidates, force us to redesign our infringing products or force us to cease some or all of our business operations, any of which could materially harm our business and could prevent us from further developing and commercializing our proposed future product candidates thereby causing us significant harm. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

Third-party owned IP relating to CRISPR/Cas9 or other related technologies necessary to develop, manufacture and commercialize viable CRISPR/Cas9 therapeutics – such as compositions of the products or components, methods of treatment, delivery technologies, chemical modifications, and analytical and manufacturing methods – could adversely impact our ability to ultimately market and sell products. Third parties may own intellectual property, including patents, that cover all or aspects of our technologies and potential products, and may be necessary for us to develop or commercialize viable products. If we are unable to successfully license, avoid or challenge such third-party intellectual property, we may not be able to develop and commercialize viable products in all or certain jurisdictions. In addition, if the intellectual property covering our products or technologies that we own or license were to be legally impaired or lost, we may be unable to realize sufficient financial returns to support the development or commercialization of our products.

Under our license agreement with Caribou, we sublicense a patent family from the Regents of the University of California and the University of Vienna that is co-owned by Dr. Emmanuel Charpentier. The outcome of recent proceedings, as well as potential future proceedings, related to this patent family may affect our ability to utilize the intellectual property sublicensed under our license agreement with Caribou.

The Broad Institute patent family includes issued patents in the U.S. and Europe that purport to cover certain aspects of the CRISPR/Cas9 genome editing platform for use on eukaryotic cells, including human cells. On June 25, 2019, the PTAB declared an interference between the UC/Vienna/Charpentier eukaryotic patent family and the Broad patent family that claim the use of the CRISPR/Cas9 technology in eukaryotic cells, including human cells. On August 26, 2019, the PTAB redeclared the interference to include additional UC/Vienna/Charpentier patent applications covering the invention that had also been found allowable by the USPTO. In this interference, the PTAB will seek to determine which research group first invented the use of the technology in eukaryotic cells and, therefore, is entitled to the patents covering the invention. If the PTAB were to conclude that UC/Vienna/Charpentier were not the first inventors, we may not have rights to this invention, which could adversely impact our ability to develop and commercialize our product candidates. If it were to succeed in the interference, the Broad could seek to assert its issued patents against us based on our CRISPR/Cas9-based activities, including commercialization. Defense of these claims, regardless of their merit, would involve substantial litigation expense,

would be a substantial diversion of management and other employee resources from our business and may impact our reputation. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. In that event, we could be unable to further develop and commercialize our product candidates, which could harm our business significantly.

In addition, other third parties, such as Vilnius University, ToolGen, Inc., MilliporeSigma (a subsidiary of Merck KGaA) and Harvard University, filed patent applications claiming CRISPR/Cas9-related inventions around or within a year after the UC/Vienna/Charpentier application was filed and may allege that they invented one or more of the inventions claimed by UC/Vienna/Charpentier before UC/Vienna/Charpentier. If the USPTO deems the scope of the claims of one or more of these parties to sufficiently overlap with the allowable claims from the UC/Vienna/Charpentier application, the USPTO could declare other interference proceedings to determine the actual inventor of such claims. In addition, UC/Vienna/Charpentier or the other third parties could seek judicial review of their inventorship claims. If UC/Vienna/Charpentier fail in defending their inventorship priority on any of these claims, we may lose valuable intellectual property rights, such as the exclusive right to use such intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, any disputes could result in substantial costs and be a distraction to management and other employees.

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

We may in the future be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor or other claims challenging the inventorship of our patents or ownership of our intellectual property (including patents and intellectual property that we in-license). For example, the UC/Vienna/Charpentier patent family that is covered by our license agreement with Caribou is co-owned by UC/Vienna and Dr. Charpentier, and our sublicense rights are derived from the first two co-owners and not from Dr. Charpentier. Therefore, our rights to these patents are not exclusive and third parties, including competitors, may have access to intellectual property that is important to our business. In addition, we may have inventorship disputes arise from conflicting obligations of collaborators, consultants or others who are involved in developing our technology and product candidates. Litigation or other legal proceedings may be necessary to defend against these and other claims challenging inventorship. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We depend on intellectual property licensed from third parties and termination or modification of any of these licenses could result in the loss of significant rights, which would harm our business.

We are dependent on patents, know-how and proprietary technology, both our own and licensed from others, including Caribou, Novartis and OSR. Any termination of these licenses, loss by our licensors of the rights they receive from others, diminution of our rights or those of our licensors, or a finding that such intellectual property lacks legal effect, could result in the loss of significant rights and could harm our ability to commercialize any product candidates. For example, UC/Vienna could challenge Caribou's rights under their agreement, including Caribou's right to sublicense its rights to others, such as Intellia, and on what terms such a sublicense would be granted, each of which could adversely impact our rights under our agreement with Caribou. Similarly, Caribou or other licensors, or other third parties from which we derive rights, could challenge the scope of our licensed rights or fields under our license agreement, which could adversely impact our exclusive rights to use CRISPR/Cas9 technology in our human therapeutics field.

For example, as discussed above**,** on September 26, 2019, we announced that an arbitration panel had issued an interim award concluding that both the structural and chemical guide RNAs modification technologies were exclusively licensed to us by Caribou pursuant to the Caribou License. After concluding that the chemical modification technology was within the scope of our exclusive license with Caribou, the arbitration panel noted that its decision could delay or otherwise adversely impact the development of these modified guide RNAs as human therapeutics. Thus, solely with respect to the particular modified guide RNAs, the arbitration panel stated that it will declare that Caribou has an equitable award, which it described as exclusive, perpetual and worldwide. Upon, and subject to the terms of, a final award, which will follow further legal proceedings between the parties, Caribou could be able to use the modified guide RNAs at issue for human therapeutics. Although the interim award has no effect on our rights or current programs nor on Caribou's obligations under the Caribou License, we cannot predict the potential implications and impact the interim award may have on our business.

Disputes have and may arise between us and our licensors, our licensors and their licensors, or us and third parties that co-own intellectual property with our licensors or their licensors, regarding intellectual property subject to a license agreement, including those relating to:

- the scope of rights, if any, granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology, products and processes infringe on, or derive from, intellectual property of the licensor that is not subject to the license agreement;
- whether our licensor or its licensor had the right to grant the license agreement, or whether they are compliant with their contractual obligations to their respective licensor(s);
- whether third parties are entitled to compensation or equitable relief, such as an injunction, for our use of the intellectual property without their authorization;
- our right to sublicense patent and other rights to third parties, including those under collaborative development relationships;
- whether we are complying with our obligations with respect to the use of the licensed technology in relation to our development and commercialization of product candidates;
- our involvement in the prosecution, defense and enforcement of the licensed patents and our licensors' overall patent strategy;
- the allocation of ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and by us and our partners; and
- the amounts of royalties, milestones or other payments due under the license agreement.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, or are insufficient to provide us the necessary rights to use the intellectual property, we may be unable to successfully develop and commercialize the affected product candidates. If we or any such licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

We depend, in part, on our licensors to file, prosecute, maintain, defend and enforce patents and patent applications that are material to our business.

Patents relating to our product candidates are controlled by certain of our licensors or their respective licensors. Each of our licensors or their licensors generally has rights to file, prosecute, maintain and defend the patents we have licensed from such licensor. If these licensors or any future licensees and in some cases, co-owners from which we do not yet have licenses, having rights to file, prosecute, maintain, and defend our patent rights fail to adequately conduct these activities for patents or patent applications covering any of our product candidates, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using or selling competing products. We cannot be certain that such activities by our licensors or their respective licensors have been or will be conducted in compliance with applicable laws and regulations or in our best interests, or will result in valid and enforceable patents or other intellectual property rights. Pursuant to the terms of the license agreements with our licensors, the licensors may have the right to control

enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents and, even if we are permitted to pursue such enforcement or defense, we cannot ensure the cooperation of our licensors or, in some cases, other necessary parties, such as the co-owners of the intellectual property from which we have not yet obtained a license. We cannot be certain that our licensors or their licensors, and in some cases, their respective co-owners, will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. For example, with respect to our sublicensed rights from Caribou to UC/Vienna/Charpentier intellectual property, UC retained the right to control the prosecution, enforcement and defense of this intellectual property in its license agreement with Caribou and, pursuant to an Invention Management Agreement, shares these responsibilities with CRISPR Therapeutics and, under certain circumstances, ERS Genomics, Ltd., as the designated managers of the intellectual property. For these reasons, UC may be unable or unwilling to prosecute certain patent claims that would be best for our product candidates, or enforce its patent rights against infringers of the UC/Vienna/Charpentier patent family.

Even if we are not a party to legal actions or other disputes involving our licensed intellectual property, an adverse outcome could harm our business because it might prevent us from continuing to license intellectual property that we may need to operate our business. In addition, even when we have the right to control patent prosecution of licensed patents and patent applications, enforcement of licensed patents, or defense of claims asserting the invalidity of those patents, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to or after our assuming control.

We may not be successful in obtaining or maintaining necessary rights to product components and processes or other technology for our product development pipeline.

The growth of our business will likely depend in part on our ability to acquire or in-license additional proprietary rights. For example, our programs may involve additional product candidates, delivery systems or technologies that may require the use of additional proprietary rights held by third parties. Our ultimate product candidates may also require specific modifications or formulations to work effectively and efficiently. These modifications or formulations may be covered by intellectual property rights held by others. We may be unable to acquire or in-license any relevant third-party intellectual property rights that we identify as necessary or important to our business operations.

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

The licensing and acquisition of third-party intellectual property rights is a competitive practice and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire.

If we are unable to successfully obtain rights to valid third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer.

We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our products or product candidates, or asserting and defending our intellectual property rights that protect our products and technologies.

We anticipate that we will file additional patent applications both in the U.S. and in other countries, as appropriate. However, we cannot predict:

- if and when any patents will issue;
- the scope, degree and range of protection any issued patents will afford us against competitors, including whether third parties will find ways to invalidate or otherwise circumvent our patents;
- whether others will apply for or obtain patents claiming aspects similar to those covered by our patents and patent applications;
- whether certain governments will appropriate our intellectual property rights and allow competitors to use them; or
- whether we will need to initiate litigation or administrative proceedings to assert or defend our patent rights, which may be costly whether we win or lose.

Composition of matter patents for biological and pharmaceutical products are generally considered to be the strongest form of intellectual property protection for those types of products, as such patents provide protection without regard to any method of use. We cannot be certain, however, that any claims in our pending or future patent applications covering the composition of matter of our product candidates will be considered patentable by the USPTO or by patent offices in foreign countries, or that the claims in any of our ultimately issued patents will be considered valid and enforceable by courts in the U.S. or foreign countries. Method of use patents protect the use of a product for the specified method, for example a method of treating a certain indication using a product. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products "off-label" for those uses that are covered by our method of use patents. Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The strength of patents in the biotechnology and pharmaceutical field can be uncertain, and evaluating the scope of such patents involves complex legal and scientific analyses. The patent applications that we own or in-license may fail to result in issued patents with claims that cover any product candidates or uses thereof in the U.S. or in other foreign countries.

Further, the patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost, in a timely manner, or in all jurisdictions. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. We may also require the cooperation of our licensors or other necessary parties, such as the co-owners of the intellectual property from which we have not yet obtained a license, in order to enforce the licensed patent rights, and such cooperation may not be provided. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The laws of foreign countries may not protect our rights to the same extent as the laws of the U.S. and we may fail to seek or obtain patent protection in all major markets. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U.S. and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we will be unable to know with certainty whether we were the first to make any inventions claimed in any patents or patent applications, or that we were the first to file for patent protection of such inventions, nor can we know whether those from whom we license patents were the first to make the inventions claimed or were the first to file.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the U.S. and abroad. There is a substantial amount of litigation as well as administrative proceedings for challenging patents, including interference, derivation, and reexamination proceedings before the USPTO and oppositions and other comparable proceedings in foreign jurisdictions, involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, and we expect this to be true for the CRISPR/Cas9 space as well. For example, a number of third parties have filed oppositions challenging the validity, and seeking the revocation, of the CRISPR/Cas9 genome editing patents granted to UC/Vienna/Charpentier by the European Patent Office to date. For example, in January 2020, the European Patent Office ("EPO") will hold a hearing on the various third parties' challenges to the validity of UC/Vienna/Charpentier's first European patent, which covers compositions comprising Cas9 and single guide RNA molecules, as well as methods of editing DNA *in vitro* or *ex vivo* using Cas9 and single guide RNAs. If UC/Vienna/Charpentier fail in defending the validity of this (or their other European patents that have similarly been opposed), we may lose valuable intellectual property rights, such as the exclusive right to use such intellectual property. Such an outcome could have a material adverse effect on our business in Europe. In addition, since the passage of the America Invents Act in 2013, U.S. law also provides for other procedures to challenge patents, including *inter partes* reviews and post-grant reviews, that add uncertainty to the possibility of challenge to our developed or licensed patents and patent applications in the future. Furthermore, for U.S. applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third-party or instituted by the USPTO to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. See the above risk factor titled "*Third-party claims of intellectual property infringement against us, our licensors or our collaborators may prevent or delay our product discovery and development efforts*."

Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to practice the invention or stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing their products to avoid being covered by our claims. If the breadth or strength of protection provided by the patent applications we hold is threatened, this could dissuade companies from collaborating with us to develop, and could threaten our ability to commercialize, product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market product candidates under patent protection would be reduced. Because patent applications in the U.S. and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates.

Our pending and future patent applications or the patent applications that we obtain rights to through in-licensing arrangements may not result in patents being issued which protect our technology or future product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the U.S. and other countries may diminish the value of our patents or narrow the scope of our patent protection.

Litigation or other administrative proceedings challenging our intellectual property, including interferences, derivation, reexamination, *inter partes* reviews and post-grant reviews, may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees. Furthermore, there could be public announcement of the results of hearings, motions or other interim proceedings or developments in any proceeding challenging the issuance, scope, validity and enforceability of our developed or licensed intellectual property. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Any of these potential negative developments could impact the scope, validity, enforceability or commercial value of our patent rights and, as a result, have material adverse effect on our business, financial condition, results of operations or prospects.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect our proprietary and confidential information. We also utilize proprietary processes for which it would be difficult to enforce patents. In addition, other elements of our product discovery and development processes involve proprietary know-how, information, or technology that is not covered by patents. Trade secrets, however, may be difficult to protect. We seek to protect our proprietary processes, in part, by entering into confidentiality agreements with our employees, consultants, outside scientific advisors, contractors, and collaborators, and we also rely on national and state laws requiring our directors, employees, contractors and collaborators to protect our proprietary information. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, outside scientific advisors, contractors, and collaborators might intentionally or inadvertently disclose our trade secret information to competitors. In addition, competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the U.S. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the U.S. and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, or misappropriation of our intellectual property by third parties, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results, and financial condition.

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

We have limited intellectual property rights outside the U.S. Filing, prosecuting, maintaining and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the U.S. can have a different scope and strength than do those in the U.S. In addition, the laws of some foreign countries, such as China, Brazil, Russia, India and South Africa, do not protect intellectual property rights to the same extent as federal and state laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the U.S. These products may compete with our products and our patents or other intellectual property rights may not be effective or adequate to prevent them from competing. In addition, in jurisdictions outside the U.S., a license may not be enforceable unless all the owners of the intellectual property agree or consent to the license. Further, patients may choose to travel to countries in which we do not have intellectual property rights or which do not enforce these rights to obtain the products or treatment from competitors in such countries.

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

We may be involved in lawsuits to protect or enforce our patents, the patents of our licensors or our licenses, which could be expensive, time-consuming, and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To cease such infringement or unauthorized use, we may be required to file patent infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding or a declaratory judgment action against us, a court may decide that one or more of our patents is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceeding could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business.

Interference or derivation proceedings provoked by third parties or brought by the USPTO may be necessary to determine the priority of inventions with respect to, or the correct inventorship of, our patents or patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Litigation, interference or derivation proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees.

Further, if a party to our licenses, either a licensee or licensor, were to breach or challenge our rights under the relevant license agreement (or if one of our licensor's own licensors were to challenge our licensor's rights), we may have to initiate or participate in a legal proceeding to enforce our rights. Any such legal proceeding could be expensive and time-consuming. In addition, if a court or other tribunal were to rule against us, we could lose key intellectual property and financial rights. Pursuing or defending against these legal claims, regardless of merits, would involve substantial legal expense and would be a substantial diversion of employee resources from our business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or contractual litigation there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or proceeding. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. For example, as discussed above**,** on September 26, 2019, we announced that an arbitration panel had issued an interim award concluding that both the structural and chemical guide RNAs modification technologies were exclusively licensed to us by Caribou pursuant to the Caribou License. Nevertheless, the arbitration panel noted that its decision could delay or otherwise adversely impact the development of these modified guide RNAs as human therapeutics. Thus, solely with respect to the particular modified guide RNAs, the arbitration panel stated that it will declare that Caribou has an equitable award, which it described as exclusive, perpetual and worldwide. Upon, and subject to the terms of, a final award, which will follow further legal proceedings between the parties, Caribou could be able to use the modified guide RNAs at issue to develop engineered CAR-T's directed at CD19 as human therapeutics. Although the interim award has no effect on our rights or current programs nor on Caribou's obligations under the Caribou License, we cannot predict the potential implications and impact the interim award may have.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court or before the USPTO or comparable foreign authority.

If we or one of our licensing partners initiate legal proceedings against a third-party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity or unenforceability are commonplace, and there are numerous grounds upon which a third-party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the U.S. or other jurisdictions, even outside the context of litigation. Such mechanisms include re-examination, *inter partes* review, post-grant review and equivalent proceedings in foreign jurisdictions, such as opposition or derivation proceedings. Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover and protect our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity of our patents, for example, we cannot be certain that there is no

invalidating prior art of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity, unpatentability and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. For example, various third parties have filed challenges to the validity of UC/Vienna/Charpentier's European patents, which cover compositions comprising Cas9 and gRNA molecules, as well as methods of editing DNA *in vitro* or *ex vivo* using Cas9 and gRNAs. If UC/Vienna/Charpentier fail in defending the validity of these patents, we may lose valuable intellectual property rights, such as the exclusive right to use such intellectual property. Such an outcome could have a material adverse effect on our business in Europe.

We may be subject to claims that our employees, directors, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies as well as academic research institutions. We may be subject to claims that we or our employees, directors, consultants, or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former employers. Litigation may be necessary to defend against these claims, which could result in money damages or a judicial order prohibiting the use of certain intellectual property. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

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

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. Although an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees, and failure to properly legalize and submit formal documents. In any such event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

We may be required to pay certain milestones and royalties under our license agreements with third-party licensors.

Under our current and future license agreements, we may be required to pay milestones and royalties based on our revenues, including sales revenues of our products, utilizing the technologies licensed or sublicensed from third parties, including Caribou, Novartis, Regeneron and OSR, and these milestones and royalty payments could adversely affect our ability to research, develop and obtain approval of product candidates, as well as the overall profitability for us of any products that we may seek to commercialize. In order to maintain our license rights under these license agreements, we will need to meet certain specified milestones, subject to certain cure provisions, in the development of our product candidates. Further, our licensors (or their licensors) or licensees may dispute the terms, including amounts, that we are required to pay under the respective license agreements. If these claims were to result in a material increase in the amounts that we are required to pay to our licensors, or in a claim of breach of the license, our ability to research, develop and obtain approval of product candidates, or to commercialize products, could be significantly impaired.

In addition, these agreements contain diligence milestones and we may not be successful in meeting all of the milestones in the future on a timely basis or at all. We will need to outsource and rely on third parties for many aspects of the clinical development, sales and marketing of our products covered under our license agreements. Delay or failure by these third parties could adversely affect the continuation of our license agreements with their third-party licensors.

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

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

Risks Related to Our Common Stock

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

In May 2016, we closed our initial public offering. Prior to this offering, there was no public market for our common stock. Although we have completed our initial public offering and shares of our common stock are listed and trading on the Nasdaq Global Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their shares at or above the prices at which they acquired their shares or sell their shares at the time they would like to sell. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

The price of our common stock historically has been volatile, which may affect the price at which you could sell any shares of our common stock.

The market price for our common stock historically has been highly volatile and could continue to be subject to wide fluctuations in response to various factors. This volatility may affect the price at which you could sell the shares of our common stock, and the sale of substantial amounts of our common stock could adversely affect the price of our common stock. Our stock price is likely to continue to be volatile and subject to significant price and volume fluctuations in response to market and other factors, including:

- the success of our or competing products or technologies;
- results of clinical trials of our product candidates or those of our competitors;
- developments or disputes concerning patent applications, issued patents or other intellectual property rights;
- regulatory or legal developments in the U.S. and other countries;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or the financial results of companies that are perceived to be similar to us;

- sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- public perception of the safety of genome editing based therapeutics;
- general economic, industry and market conditions; and
- the other factors described in this *Risk Factors* section.

In addition, companies trading in the stock market in general, and in the Nasdaq Global Market in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. In the past, following periods of volatility in the market, securities class-action litigation has often been instituted against companies. Such litigation, if instituted against us, could result in substantial costs and diversion of management's attention and resources, which could materially and adversely affect our business, financial condition, results of operations and growth prospects.

Our principal stockholders and management own a significant percentage of our stock and, if they choose to act together, will be able to control or exercise significant influence over matters subject to stockholder approval.

As of December 31, 2019, our executive officers, directors, 5% or greater stockholders and their affiliates beneficially owned approximately 63% of our outstanding voting stock. These stockholders may have the ability to influence us through their ownership positions. These stockholders may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We have broad discretion over the use of our cash and cash equivalents and may not use them effectively.

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

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our equity incentive plans, could result in additional dilution of the percentage ownership of stockholders and could cause our stock price to fall.

We will need additional capital in the future to continue our planned operations in addition to the proceeds we received from our initial public offering ("IPO") in May 2016 and follow-on public offering in November 2017. To the extent we raise additional capital by issuing equity securities, our stockholders may experience substantial dilution. We may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. These sales may also result in material dilution to our existing stockholders, and new investors could gain rights superior to our existing stockholders.

On October 12, 2018, we filed a Shelf Registration Statement on Form S-3 (the "2018 Shelf") with the SEC in relation to the registration of common stock, preferred stock, warrants and units of any combination thereof for the purposes of selling, from time to time, our common stock, convertible securities or other equity securities in one or more offerings. We also simultaneously entered into an Open Market Sale Agreement (the "2018 Sales Agreement") with Jefferies LLC (the "Sales Agent"), to provide for the offering, issuance and sale of up to an aggregate amount of $100.0 million of our common stock from time to time in "at-the-market" offerings under the 2018 Shelf and subject to the limitations thereof. We have paid the Sales Agent cash commissions of 3.0% of the gross proceeds of sales of common stock under the 2018 Sales Agreement. In November 2018, we issued 1,659,300 shares of our common stock at $18.00 per share in accordance with the 2018 Sales Agreement for net proceeds of $28.5 million, after payment of cash commissions to the Sales Agent and approximately $0.4 million related to legal, accounting and other fees in connection with the sales. During the twelve months ended December 31, 2019, we issued an additional 4,231,348 shares of our common stock, in a series of sales, at an average price of $16.57 per share, in accordance with the 2018 Sales Agreement, for aggregate net proceeds of $67.8 million, after payment of cash commissions to the Sales Agent and approximately $0.2 million related to legal, accounting and other fees in connection with the sales. As of December 31, 2019, there were no shares of common stock eligible for sale under the 2018 Sales Agreement.

On August 23, 2019, we filed a Registration Statement on Form S-3, as amended (the "2019 Shelf") with the SEC, which was declared effective on September 12, 2019 (File No. 333-233448) in relation to the registration of common stock, preferred stock, debt securities, warrants and units of any combination thereof. We also simultaneously entered into an Open Market Sale Agreement (the "2019 Sales Agreement") with the Sales Agent, to provide for the offering, issuance and sale of up to an aggregate amount of $150.0 million of our common stock from time to time in "at-the-market" offerings under the 2019 Shelf and subject to the limitations thereof. We will pay to the Sales Agent cash commissions of 3.0% of the gross proceeds of sales of common stock under the 2019 Sales Agreement. In December 2019, we issued 287,231 shares of our common stock at an average price of $16.48 per share in accordance with the 2019 Sales Agreement for aggregate net proceeds of $4.4 million, after payment of cash commissions to the Sales Agent and approximately $0.2 million related to legal, accounting and other fees in connection with the sales. In addition, sales of a substantial number of shares of our outstanding common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock. Persons who were our stockholders prior to our IPO continue to hold a substantial number of shares of our common stock that many of them are now able to sell in the public market. Significant portions of these shares are held by a relatively small number of stockholders. Sales by our stockholders of a substantial number of shares, or the expectation that such sales may occur, could significantly reduce the market price of our common stock.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us difficult, limit attempts by our stockholders to replace or remove our current management and adversely affect our stock price.

Provisions of our certificate of incorporation and by-laws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our stock. Among other things, the certificate of incorporation and by-laws:

- permit the board of directors to issue up to 5,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate;
- provide that the authorized number of directors may be changed only by resolution of the board of directors;
- provide that all vacancies, including newly created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- divide the board of directors into three classes;
- provide that a director may only be removed from the board of directors by the stockholders for cause;

- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders, and may not be taken by written consent;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner, and meet specific requirements as to the form and content of a stockholder's notice;
- prevent cumulative voting rights (therefore allowing the holders of a plurality of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose);
- require that, to the fullest extent permitted by law, a stockholder reimburse us for all fees, costs and expenses incurred by us in connection with a proceeding initiated by such stockholder in which such stockholder does not obtain a judgment on the merits that substantially achieves the full remedy sought;
- provide that special meetings of our stockholders may be called only by the chairman of the board, our chief executive officer (or president, in the absence of a chief executive officer) or by the board of directors; and
- provide that stockholders will be permitted to amend the bylaws only upon receiving at least two-thirds of the total votes entitled to be cast by holders of all outstanding shares then entitled to vote generally in the election of directors, voting together as a single class.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with any "interested" stockholder for a period of three years following the date on which the stockholder became an "interested" stockholder.

Our certificate of incorporation and by-laws provide that the Court of Chancery of the State of Delaware will be the exclusive forum for certain disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation and by-laws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware is the sole and exclusive forum for any state law claims for any derivative action or proceeding brought on our behalf alleging state law claims, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our by-laws, any action to interpret, apply, enforce, or determine the validity of our certificate of incorporation or bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision does not apply to claims arising under the Exchange Act or the Securities Act. The choice of forum provision may impose additional litigation costs on stockholders in pursuing the claims identified above, particularly if the stockholders do not reside in or near the State of Delaware. Additionally, the choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation and by-laws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition. The Court of Chancery of the State of Delaware may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

We incur significant costs as a result of operating as a public company, and our management is required to devote substantial time to compliance initiatives and corporate governance practices.

As a public company, and particularly since we are no longer an "emerging growth company" under applicable SEC regulations, we incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002 ("Section 404"), we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. We conduct a process each year to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we dedicate internal resources, engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

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

The trading market for our common stock will depend, in part, on the research and reports that securities or industry analysts publish about us or our business. Securities and industry analysts may not publish an adequate amount of research on us, which may negatively impact the trading price for our stock. In addition, if one or more of the analysts who cover us downgrade our stock or publish inaccurate or unfavorable research about our business, our stock price would likely decline. Further, if our operating results fail to meet the forecasts of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, demand for our stock could decrease, which might cause our stock price and trading volume to decline.

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

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

We could be subject to significant legal proceedings which may adversely affect our results of operations or financial condition.

We are subject to the risk of litigation, derivative claims, securities class actions, regulatory and governmental investigations and other proceedings, including proceedings arising from investor dissatisfaction with us or our performance. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years. In addition, if any individuals acting on our behalf fails to satisfy his or her relevant legal or contractual duties, we could have liability to third-parties, including the government or investors. If any claims were brought against us and resulted in a finding of substantial legal liability, the finding could materially adversely affect our business, financial condition or results of operations or cause significant reputational harm to us, which could seriously adversely impact our business. Allegations of improper conduct by private litigants or regulators, regardless of veracity, also may harm our reputation and adversely impact our ability to grow our business. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

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

The laws and rules dealing with U.S. federal, state and local income taxation are routinely being reviewed and modified by governmental bodies, officials and regulatory agencies, including the Internal Revenue Service and the U.S. Treasury Department. Since we were founded in 2014, many such changes have been made and changes are likely to continue to occur in the future. It cannot be predicted whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or issued, that could result in an increase in our or our shareholders' tax liability.

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

We have incurred substantial losses during our history and do not expect to become profitable in the near future, and we may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. As of December 31, 2019, we had federal and state NOLs of $229.9 million and $236.8 million, respectively, which begin to expire in 2034. As of December 31, 2019, we had federal and state research and development and other credit carryforwards of approximately $12.6 million and $8.7 million, which begin to expire in 2035 and 2031, respectively. Under Sections 382 and 383 of the Code, if a corporation undergoes an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a three-year period, the corporation's ability to use its pre-change NOLs, and other pre-change tax attributes (such as research and development tax credits) to offset its post-change income or taxes may be limited. We may have experienced ownership changes in the past and may experience ownership changes in the future as a result of our initial public offering in May of 2016, follow-on offerings and/or subsequent shifts in our stock ownership (some of which shifts are outside our control). As a result, if we earn net taxable income, our ability to use our pre-change NOLs and research and development tax credits to offset such taxable income and income tax, respectively, could be subject to limitations. Similar provisions of state tax law may also apply. As a result, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes. NOLs generated in taxable years ending after December 31, 2017 are not subject to expiration.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are located at 40 Erie Street in Cambridge, Massachusetts, where we occupy approximately 65,000 square feet of office and laboratory space. We have a ten year lease agreement expiring in September 2026, with an option to terminate the lease at the end of the sixth year and an option to extend the term of the lease for an additional three years. In addition, we lease and sublease approximately 24,000 square feet of office and laboratory space at 130 Brookline Street in Cambridge, Massachusetts, which expire in 2025 and 2021, respectively.

Item 3. Legal Proceedings

In the ordinary course of business, we are from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation related to intellectual property ("IP"), commercial arrangements and other matters, including the matter described below. The outcome of any such legal proceedings, regardless of the merits, is inherently uncertain. In addition, litigation and related matters are costly and may divert the attention of our management and other resources that would otherwise be engaged in other activities. If we were unable to prevail in any such legal proceedings, our business, results of operations, liquidity and financial condition could be adversely affected.

Caribou Intellectual Property Arbitration

On September 26, 2019, we announced that the arbitration panel issued an interim award concluding that both the structural and chemical guide RNAs modification technologies were exclusively licensed to us by Caribou Biosciences, Inc. ("Caribou") pursuant to the 2014 license agreement with Caribou (the "Caribou License"). After concluding that the chemical modification technology was within the scope of our exclusive license from Caribou, the arbitration panel nevertheless noted that its decision could delay or otherwise adversely impact the development of these modified guide RNAs as human therapeutics. It also noted that we currently are not using these modified guide RNAs in any of our active programs. Thus, solely with respect to the particular modified guide RNAs, the arbitration panel stated that it will declare that Caribou has an equitable "leaseback", which it described as exclusive, perpetual and worldwide (the "Caribou Award"). The panel instructed the parties to negotiate the terms of the Caribou Award, including Caribou's future payments to us for the same, but the parties' negotiations reached an impasse.

On February 6, 2020, after considering additional submissions from the parties, the panel clarified that the Caribou Award is limited to a particular on-going Caribou program, which seeks to develop a CAR-T product directed at CD19. The panel instructed the parties to seek to negotiate terms based on this scope. Accordingly, the Caribou Award will be subject to terms, including Caribou's future payments to us to be negotiated by the parties or, if unsuccessful, adjudicated in additional arbitration or judicial proceedings.

Pursuant to the September 2019 interim award, the Caribou Award by the panel does not include the structural guide modifications IP at issue in the arbitration, any other IP exclusively licensed or sublicensed by Caribou to us under the Caribou License (including but not limited to the foundational CRISPR/Cas9 IP co-owned by the Regents of the University of California, University of Vienna and Dr. Emmanuelle Charpentier), or any other of our IP.

Upon, and subject to the terms of, a final award, which will follow further arbitration or legal proceedings, Caribou could be able to use the modified guide RNAs at issue for CAR-T cell human therapeutics directed at CD19. Either we or Caribou may challenge the arbitration panel's decisions under limited circumstances.

Other than with regards to the technologies in dispute, the interim award has no effect on our rights or Caribou's obligations under the Caribou License. The interim award has no impact on any of our current programs, although it could impact the 2014 Novartis Agreement.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Our common stock is traded on the Nasdaq Global Market under the symbol "NTLA".

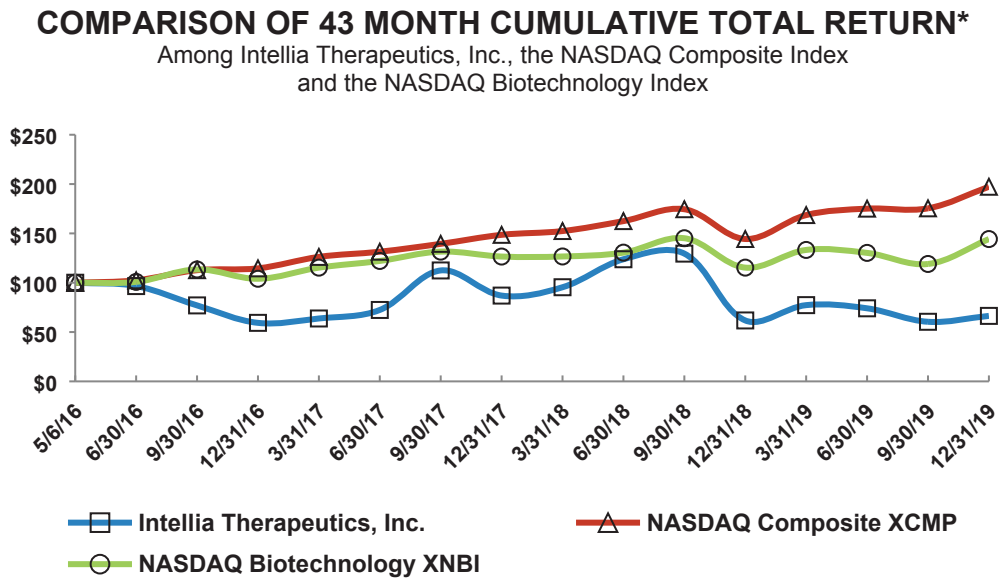
As of February 21, 2020, the number of holders of record of our common stock was 22. The actual number of holders of our common stock is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This holders of record number also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid cash dividends on our capital stock. We intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay cash dividends to our stockholders in the foreseeable future.

Stock Performance Graph

The following graph shows a comparison from May 6, 2016, the first date that shares of our common stock were publicly traded, through December 31, 2019, of the cumulative total return on an assumed investment of $100.00 in cash in our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index for the same period. Such returns are based on historical results and are not intended to suggest future performance. Data for the Nasdaq Composite Index and the Nasdaq Biotechnology Index assume reinvestment of dividends.



The performance graph in this Item 5 is not deemed to be "soliciting material" or to be "filed" with the Securities and Exchange Commission for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities under that Section, and shall not be deemed incorporated by reference into any of our filings under the Securities Act of 1933 or the Securities Exchange Act of 1934, except to the extent we specifically incorporate it by reference into such a filing.

Equity Compensation Plans

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

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report.

Item 6. Selected Financial Data

The following selected financial data has been derived from our consolidated financial statements. The information set forth below should be read in conjunction with Item 7. *Management's Discussion and Analysis of Financial Condition and Results of Operations* and with our consolidated financial statements and notes thereto included elsewhere in this document.

	Year Ended December 31,				
	2019	2018	2017	2016	2015
	(in thousands except per share data)				
Consolidated Statements of Operations Data:					
Collaboration revenue	$ 43,103	$ 30,434	$ 26,117	$ 16,479	$ 6,044
Operating expenses:					
Research and development	108,413	89,115	67,647	31,840	11,170
General and administrative	41,058	32,189	28,025	16,798	8,283
Total operating expenses	149,471	121,304	95,672	48,638	19,453
Operating loss	(106,368)	(90,870)	(69,555)	(32,159)	(13,409)
Interest income	6,835	5,527	2,012	525	-
Loss before income taxes	(99,533)	(85,343)	(67,543)	(31,634)	(13,409)
Income tax benefit	-	-	-	-	1,012
Net loss	$ (99,533)	$ (85,343)	$ (67,543)	$ (31,634)	$ (12,397)
Net loss per share or common unit, basic and diluted	$ (2.11)	$ (1.98)	$ (1.88)	$ (1.42)	$ (51.02)
Weighted average shares or common units outstanding, basic and diluted	47,247	43,069	36,006	22,222	243

	As of December 31,				
	2019	2018	2017	2016	2015
	(in thousands)				
Consolidated Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$ 284,472	$ 314,059	$ 340,678	$ 273,064	$ 75,816
Working capital (1)	253,848	284,405	323,471	250,576	66,931
Total assets	334,280	347,315	376,235	298,969	82,139
Deferred revenue	28,810	55,932	65,299	78,287	10,312
Convertible preferred stock	-	-	-	-	88,557
Total stockholders' equity	269,881	277,920	300,597	209,837	(21,201)

(1) We define working capital as current assets less current liabilities.

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

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

Information pertaining to fiscal year 2017 was included in the Company's Annual Report on Form 10-K for the year ended December 31, 2018 on pages 91 through 104 under Part II, Item 7, "Management's Discussion and Analysis of Financial Position and Results of Operations," which was filed with the Securities and Exchange Commission (the "SEC") on February 27, 2019.

Management Overview

Intellia Therapeutics, Inc. ("we," "us," "our," "Intellia," or the "Company") is a leading genome editing company focused on developing curative therapeutics utilizing a biological tool known as CRISPR/Cas9, which stands for Clustered, Regularly Interspaced Short Palindromic Repeats ("CRISPR")/CRISPR associated 9 ("Cas9"). This is a technology for genome editing, the process of altering selected sequences of genomic deoxyribonucleic acid ("DNA"). We believe that CRISPR/Cas9 technology has the potential to transform medicine by editing disease-associated genes with a single treatment course, and that it also can be used to create novel engineered cell therapies that can replace a patient's diseased cells or effectively target various cancers and autoimmune diseases. We are leveraging our leading scientific expertise, clinical development experience and intellectual property ("IP") position to unlock a broad set of therapeutic applications for CRISPR/Cas9 genome editing and to develop a potential new class of therapeutic products.

Our mission is to build a company to develop curative genome editing treatments that can positively transform the lives of people living with severe and life-threatening disease. We believe we can deliver on our mission and provide long-term benefits for all of our stakeholders by focusing on four key elements:

- Develop curative CRISPR/Cas9 based medicines;
- Advance our science to help more patients;
- Foster an environment that is the best place to make therapies; and
- Focus on long-term sustainability.

Our strategy is to build a full-spectrum genome editing company, by leveraging our CRISPR/Cas9 platform across two areas: *in vivo* applications, in which CRISPR/Cas9 is the therapy, delivered to target cells within the body; and *ex vivo* applications, in which CRISPR/Cas9 creates the therapy of engineered human cells. All of our revenue to date has been collaboration revenue. Since our inception and through December 31, 2019, we have raised an aggregate of approximately $652.6 million to fund our operations, of which $154.5 million was through our collaboration agreements, $170.5 million was from our initial public offering and concurrent private placements, $141.0 million was from a follow-on offering, $101.6 million was from at-the-market offerings and $85.0 million was from the sale of convertible preferred stock.

The breadth of our CRISPR/Cas9 platform and delivery technology allows us to pursue a multitude of therapeutic targets/clinical indications. Specifically, we can target diseases that have the potential to be addressed by directly editing specific genes (i.e., gene knockout, repair, or insertion) as well as diseases that may be targeted by genetically engineered cell therapies. The successful treatment of these disorders may require various types of genome edits, CRISPR/Cas9 elements and DNA templates. We have assembled multiple *in vivo* and engineered cell therapy capabilities into a pipeline that reflects our full-spectrum approach and leverages the modularity inherent in our platform.

Our diversified pipeline includes *in vivo* development programs targeting genetic diseases, including transthyretin amyloidosis ("ATTR"), which we are co-developing with Regeneron Pharmaceuticals, Inc. ("Regeneron"), and hereditary angioedema ("HAE"). Our pipeline also includes *ex vivo* programs consisting of two separate efforts: 1) a set of proprietary programs focused on engineered cell therapies to treat various cancers and autoimmune diseases including our lead *ex vivo* program to target Wilms' Tumor 1 ("WT1") for acute myeloid leukemia ("AML"); and 2) partnered programs developed in collaboration with Novartis Institutes for BioMedical Research, Inc. ("Novartis"), focused on chimeric antigen receptor ("CAR") T ("CAR-T") cells, hematopoietic stem cells ("HSCs"), the stem cells from which all of the various types of blood cells originate, and stem cells in the eye, or ocular stem cells ("OSCs").

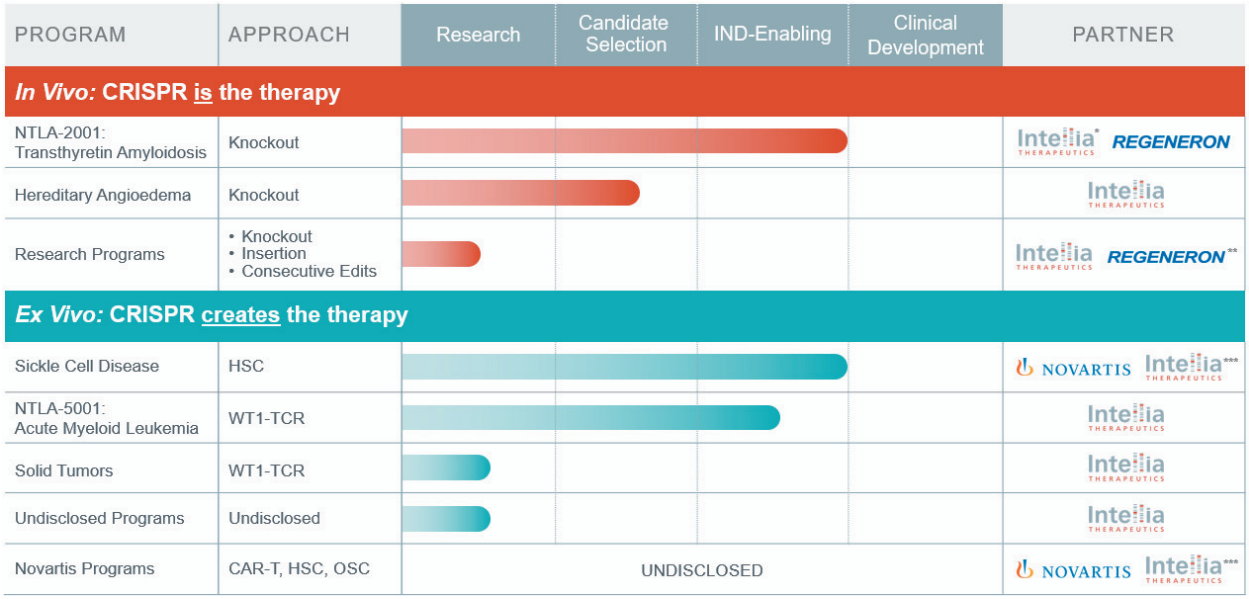
Our Pipeline

Our diversified pipeline includes *in vivo* and *ex vivo* programs. Our *in vivo* programs focus on treating patients that have significant unmet medical needs due to diseases attributable to genes expressed in the liver – ATTR (which we are co-developing with Regeneron) and HAE. Delivery plays a key role in our *in vivo* therapeutic approach. We have shown in animal models that our proprietary LNP delivery technology, which encapsulates the therapeutic Cas9 messenger RNA ("mRNA") and guide RNA ("gRNA") into lipid nanoparticles ("LNPs"), can systemically deliver these therapeutic components to the liver.

For *ex vivo* applications, our wholly owned programs focus on next-generation, engineered cell therapy solutions that utilize antigen specific T cell receptors ("TCRs"). The cells to be modified *ex vivo* can come from the individual patient (autologous source) or from another individual (allogeneic source). Our goal for the *ex vivo* pipeline is to move from autologous to allogeneic therapies, and from liquid to solid tumors.

We believe our full spectrum approach to *in vivo* and *ex vivo* programs positions us to build a pipeline across a wide range of indications.

The following table summarizes the status of our most advanced programs:



In Vivo *Programs*

Our selection criteria 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 effective treatments are absent, limited or unduly burdensome. Our initial *in vivo* indications target genetic liver diseases, including ATTR and HAE. Our current efforts on *in vivo* delivery focus on the use of LNPs for delivery of the CRISPR/Cas9 complex to the liver.

Transthyretin Amyloidosis – ("ATTR")

ATTR is a progressive and fatal disorder resulting from deposition of insoluble amyloid fibrils into multiple organs and tissues leading to systemic failure. Blood-borne transthyretin ("TTR") protein is produced by hepatocytes and normally circulates as a soluble homotetramer that facilitates transport of vitamin A, via retinol binding protein, as well as the thyroid hormone, thyroxine. Mutations in the *TTR* gene lead to the production of TTR proteins that are destabilized in their tetramer form. These tetramers more readily dissociate into the monomeric form, and thence to an aggregative form that results in amyloid deposits in tissues. These deposits cause damage in those tissues, resulting in a disorder known as hereditary TTR amyloidosis ("hATTR"). Over 120 different genetic mutations are currently known to cause hATTR.

Deposits of TTR amyloid in the heart, nerves and/or other tissues can lead to diverse disease manifestations, including two main hereditary forms – hATTR with polyneuropathy ("hATTR-PN"), and hATTR with cardiomyopathy ("hATTR-CM"). Typical onset of disease symptoms is during adulthood and can be fatal within 2 to 15 years. Estimates suggest that approximately 50,000 patients suffer from hATTR worldwide.

In addition to the hereditary forms described above, ATTR can also develop spontaneously in the absence of any *TTR* gene mutation. This wild-type ATTR ("wtATTR") is increasingly being recognized as a significant and often undiagnosed cause of heart failure in the elderly and is the subject of active investigation. Recent estimates suggest that, globally, between 200,000 and 500,000 people may suffer from wtATTR with cardiomyopathy ("wtATTR-CM").

In non-human primate ("NHP") studies, we have demonstrated our ability to reduce circulating TTR protein to estimated therapeutically relevant levels after a single systemic administration of LNPs containing our CRISPR/Cas9 complex. In December 2019, we completed a year-long durability study of our lead LNP formulation, maintaining an average reduction of more than 95% of serum TTR protein after a single dose in NHPs. The data from our various NHP studies has also demonstrated the transient nature of Intellia's proprietary modular LNP delivery system, which was rapidly cleared from circulation, with all CRISPR/Cas9 complex undetectable in blood and liver within ten days of administration.

On August 1, 2019, we announced that we conducted our pre-Investigational New Drug ("IND") meeting with the U.S. Food and Drug Administration ("FDA"), initiated IND-enabling toxicology studies, expect to submit an IND application for NTLA-2001, our lead candidate for the treatment of ATTR, in mid-2020 and anticipate dosing the first patients in the second half of 2020. NTLA-2001 is being co-developed with Regeneron pursuant to a license and collaboration agreement and a Co-Development and Co-Promotion agreement directed to ATTR (the "ATTR Co/Co") with Regeneron under which we are the lead development and commercialization party. Under the terms of the ATTR Co/Co, Regeneron was reimbursing us for 50% of the costs and has been entitled to 50% of the profits. On December 13, 2019, Regeneron informed us that it would exercise its right under the ATTR Co/Co to modify its shares of worldwide development costs and profits from 50% to 25%, effective six months after its notice. Pursuant to the ATTR Co/Co, Regeneron funded approximately 50% of the program's development costs through 2019. Starting June 2020 and thereafter, Regeneron will share approximately 25% of worldwide development costs and commercial profits for the ATTR program.

Hereditary Angioedema – ("HAE")

HAE is a rare genetic disorder characterized by recurrent, painful and unpredictable episodes of severe swelling. The most common areas of the body to develop swelling are the limbs, face, intestinal tract and airway. Minor trauma or stress may trigger an attack but swelling often occurs without a known trigger. Episodes involving the intestinal tract cause severe abdominal pain, nausea and vomiting. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. The disease is caused by increased levels of bradykinin, a protein which leads to swelling. Most patients with HAE have a deficiency of C1 esterase inhibitor ("C1-INH") protein, which normally prevents the unregulated release and buildup of bradykinin. HAE is estimated to affect 1 in 50,000 people, with an estimated 11,000 to 21,500 diagnosed HAE patients in the U.S. and Europe.

Currently there are multiple therapies approved to treat HAE, including acute and prophylactic approaches. Acute treatments are used to treat patients who are experiencing an attack. Prophylactic treatments are used to reduce the number of attacks that a patient may experience. Prophylactic treatments have proven to be effective in reducing the number of attacks for most patients, though some patients still experience breakthrough attacks and such treatment options require regular injections which can be associated with significant treatment burden and impact on quality of life.

Using our modular LNP delivery system, we aim to knock out the *kallikrein B1 ("KLKB1"*) gene with a single course of treatment to reduce the spontaneous activation of biological pathways responsible for generating bradykinin and thereby ameliorate the frequency and intensity of HAE attacks. We believe *KLKB1* knockout to be safe, as humans with prekallikrein deficiency appear to have no known health effects. In addition, inhibition of kallikrein activity has proven to be a clinically effective approach as a prophylactic treatment for HAE.

In February 2020, we shared data demonstrating that the knockout of *KLKB1* produced in NHPs resulted in a 90% reduction in kallikrein activity following a single dose. The reduction of kallikrein activity observed corresponds to the reduced enzymatic levels in patients that meaningfully impact HAE attack rates (Source: Banerji et al., NEJM, 2017). This kallikrein activity reduction was sustained for at least five months in an ongoing study, in a highly reproducible manner observed across both rodent and NHP studies. We expect to nominate a development candidate for the treatment of HAE in the first half of 2020. The *KLKB1* HAE program is subject to an option by Regeneron to enter into a Co/Co agreement prior to the initiation of IND-enabling studies, in which we would remain the lead party.

Ex Vivo *Programs*

We are independently researching and developing proprietary engineered cell therapies to treat various oncological and autoimmune diseases, for example TCR-engineered T cells for immuno-oncology applications and engineered regulatory T cells for autoimmune disorders. Our diverse product strategy includes multiple elements. In particular:

- We are exploring non-CAR-T cellular approaches that use immune cells, including T cells expressing recombinant TCRs, for oncology indications. For example, in our existing collaboration with IRCCS Ospedale San Raffaele ("OSR"), Milan, a leading European research-university hospital, we have identified optimized TCRs recognizing a tumor target, WT1, that could be used to treat a variety of cancers.
- We seek to develop allogeneic cellular therapies, which are those derived from unmatched donors and modified outside of the human body to allow them to be administered to an unrelated patient.
- We are also exploring methods to apply CRISPR/Cas9 editing to CD4 immune cells to induce a non-reverting regulatory T cell phenotype, to create therapies that address autoimmune diseases.

In addition, our partner Novartis is developing therapies using CAR-T cells for oncology indications, as well as HSC and OSC-based therapies.

Acute Myeloid Leukemia ("AML")

AML includes a heterogenous group of blood cancers arising from the malignant expansion of hematopoietic cells of the myeloid lineage. AML is associated with weakness, fatigue and bleeding resulting from the depletion of healthy myeloid cells, and is typically rapidly progressive and fatal without immediate treatment. AML is an aggressive and hard-to-treat cancer, resulting in less than 30% of patients living more than five years after diagnosis. AML is the most common acute leukemia in adults and is associated with the largest number of annual deaths from leukemia in the U.S. It is estimated that there have been nearly 11,000 deaths due to AML, as well as over 21,000 new AML cases in the U.S. in 2019. While AML can occur at any age, the prevalence of the disease increases with age, resulting in a median age at diagnosis of 67 years.

Over the past several years, new treatments have emerged for AML with different mechanisms of action. While these treatments have led to improvements in response rates and in some cases increased overall survival, the outcomes demonstrated thus far have been incremental in nature and long-term outcomes in AML continue to be extremely poor.

We have nominated NTLA-5001 as our first engineered T cell therapy development candidate for the treatment of AML, utilizing our TCR-directed approach to target the WT1 intracellular antigen. Our WT1-directed TCR T-cell therapy aims to develop a broadly applicable treatment for AML, regardless of mutational background of a patient's leukemia. This approach employs CRISPR/Cas9 complexes to knock out and replace the endogenous TCR with a natural, high affinity therapeutic TCR. The resulting cells are engineered to be capable of specific and potent killing of AML blasts without bone marrow cell toxicity. In February 2020, we presented data demonstrating that the selection of a natural, high-affinity TCR, in combination with our CRISPR-enabled engineering and targeted insertion, results in an engineered T cell capable of specific and potent killing of primary AML blasts. Importantly, our studies showed that CRISPR-enabled engineering overcomes key challenges of traditional TCR approaches, such as mispairing between therapeutic and endogenous TCR, therefore creating a more homogenous T cell product. The cells engineered with our lead WT1 TCR also exhibited no detectable off-target reactivity to bone marrow cells, which express WT1 at low levels. We continue to advance good manufacturing practices ("GMP") manufacturing-related development activities in support of a Phase I clinical trial. We expect to submit an IND application for the use of NTLA-5001 to treat AML in the first half of 2021.

Research Collaboration with Novartis

Under our collaboration agreement with Novartis, we received an upfront technology access payment from Novartis of $10.0 million, and we have received an additional $50.0 million, in aggregate, in additional technology access fees and research payments during the five-year collaboration term. In December 2019, the research term ended, although the 2014 Novartis Agreement remains in effect. Accordingly, Novartis has selected various CAR-T cell, HSC and OSC targets for continued development, for which we will be eligible to receive milestone and royalty payments in the future. Further, 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 collaboration with Novartis, see the section below entitled "Collaborations - Novartis."

CAR-T Cell Program

In 2017, the first CAR-T cell products, including Novartis' *Kymriah*, were approved by the FDA to treat certain oncological indications such as pediatric acute lymphoblastic leukemia and Non-Hodgkins Lymphoma. Additional therapies are being developed for blood cancers such as AML, multiple myeloma and chronic lymphocytic leukemia, as well as several solid-tumor cancers. In CAR-T cell therapy, naturally-occurring immune cells, specifically T cells, are modified *ex vivo* by inserting a CAR into the T cells, thereby redirecting their response towards cancer cells.

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

- 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.
- 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 knock out 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.

Novartis is progressing CRISPR/Cas9-edited CAR-T cells directed to its selected CAR targets. The target selection process was completed by the end of 2019, and all non-selected CAR targets are available for our development.

HSC Program

HSCs are the stem cells from which all of the various types of blood cells originate. The HSCs present in transplanted bone marrow, mobilized peripheral blood or cord blood can repopulate a patient's blood system. There are multiple potential opportunities for treating patients using engineered HSCs, including treating 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; 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. In 2019, Novartis completed IND-enabling studies in support of a potential IND on a program targeting sickle cell disease that leveraged our CRISPR/Cas 9 technology. We are entitled to receive a $5.0 million payment related to this regulatory milestone upon filing the IND. During the research collaboration with Novartis that concluded in December 2019, we pursued a number of potential gene targets and therapeutic indications with Novartis. From those targets, Novartis has selected a limited number of HSC targets for development into human therapeutics. Novartis' ability to select additional HSC therapeutic targets under the agreement expired in December 2019.

OSC Program

In 2018 we announced an expansion of our existing cell therapy collaboration with Novartis to include the *ex vivo* development of innovative cell therapies using certain OSCs. As part of the updated collaboration terms, Novartis obtained the right to develop CRISPR/Cas9-based products for a limited number of targets using these stem cells. Novartis' selection period for additional OSC targets expired in December 2019. We received a one-time $10.0 million cash payment and, consistent with the original collaboration agreement, we are also eligible to receive downstream success-based milestones and royalties. We retained rights to all other *in vivo* and *ex vivo* applications of CRISPR/Cas9, including for eye disorders.

Other Research Programs

We are pursuing a number of *in vivo* and *ex vivo* genome editing programs. Within our *in vivo* research efforts, we continue to work on programs such as primary hyperoxaluria Type 1 ("PH1"), alpha-1 antitrypsin deficiency ("AATD"), and Hemophilia B, which leverage our capabilities to knockout, insert and make consecutive edits to the genome. We are also investigating delivery strategies that target tissues outside of the liver.

Within our *ex vivo* research efforts, we are developing engineered cell therapies to treat a range of hematological and solid tumors. We are pursuing modalities, such as TCR, with broad potential in multiple indications. We continue to advance efforts to move from autologous to allogeneic and from liquid to solid tumors.

Collaborations

Novartis

As described in "Collaborations - Novartis Institutes for BioMedical Research, Inc.," in December 2014, we entered into a strategic license and collaboration agreement with Novartis (the "2014 Novartis Agreement"), primarily focused on the research of new *ex vivo* CRISPR/Cas9-edited therapies using CAR-T cells and HSCs.

In December 2018, we entered into an amendment to this agreement with Novartis (the "Novartis Amendment"), which expanded the scope of the 2014 Novartis Agreement to include the *ex vivo* development of CRISPR/Cas9-based cell therapies using limbal stem cells, a type of OSC, primarily against gene targets selected by Novartis in exchange for a one-time payment of $10.0 million which we received in December 2018. In December 2019, per the terms of the 2014 Novartis Agreement, the research term ended, although the 2014 Novartis Agreement remains in effect. As provided in the agreement, Novartis has selected various CAR-T cell, HSC and OSC targets for continued development, for which we will be eligible to receive milestone and royalty payments in the future.

Through December 31, 2019, we had recorded a total of $57.4 million in cash and accounts receivable under the 2014 Novartis Agreement and Novartis Amendment. Through December 31, 2019, we have recognized $57.4 million of collaboration revenue, including $18.5 million and $10.3 million in the years ended December 31, 2019 and 2018, respectively, in the consolidated statements of operations and comprehensive loss related to this agreement. As of the periods ended December 31, 2019 and 2018, we had accounts receivable of $1.0 million and $6.0 million, respectively, related to this agreement. As of December 31, 2019, we had no deferred revenue related to this agreement. As of December 31, 2018, we had deferred revenue of $14.5 million related to this agreement.

Regeneron

As described in "Collaborations - Regeneron Pharmaceuticals, Inc.," in April 2016, we entered into a license and collaboration agreement with Regeneron (the "Regeneron Agreement"). The Regeneron Agreement has two principal components: (i) a product development component under which the parties will research, develop and commercialize CRISPR/Cas-based therapeutic products primarily focused on genome editing in the liver, and (ii) a technology collaboration component, pursuant to which the parties will engage in research and development activities aimed at discovering and developing novel technologies and improvements to CRISPR/Cas technology to enhance our genome editing platform. Under the Regeneron 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.

Through December 31, 2019, we have recorded a $75.0 million upfront payment and $24.1 million for research and development services under the Regeneron agreement. Through December 31, 2019, we have recognized $70.3 million of collaboration revenue, including $24.6 million and $20.1 million in the years ended December 31, 2019 and 2018, respectively. This includes $12.0 million and $7.5 million, respectively, representing payments due from Regeneron pursuant to the ATTR Co/Co agreement, which is accounted for under Accounting Standards Codification ("ASC") 808, *Collaborative Arrangements* ("ASC 808"). As of December 31, 2019 and 2018, we had accounts receivable of $3.6 million and $1.5 million, respectively, and deferred revenue of $28.8 million and $41.4 million, respectively, related to this agreement.

Financial Overview

Collaboration Revenue

Our revenue consists of collaboration revenue, including amounts recognized related to upfront technology access payments for licenses, technology access fees, research funding and milestone payments earned under our collaboration and license agreements with Novartis and Regeneron.

Research and Development

Research and development expenses consist of expenses incurred in performing research and development activities, including compensation and benefits, which includes equity-based compensation, for full-time research and development employees, facility-related expenses, overhead expenses, reagents, laboratory supplies, consumables and contract research services.

General and Administrative

General and administrative expenses consist primarily of salaries and benefits, including equity-based compensation, for our executive, finance, legal, business development and support functions. Also included in general and administrative expenses are allocated facility-related costs not otherwise included in research and development expenses, travel expenses and professional fees for auditing, tax and legal services, including IP-related legal services, and other consulting fees and expenses.

Interest Income

Interest income is income earned on our cash equivalents and marketable securities.

Results of Operations

Comparison of Years Ended December 31, 2019 and 2018

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018:

	Year Ended December 31,		Period-to-Period Change
	2019	2018	
Collaboration revenue	$ 43,103	$ 30,434	$ 12,669
Operating expenses:			
Research and development	108,413	89,115	19,298
General and administrative	41,058	32,189	8,869
Total operating expenses	149,471	121,304	28,167
Operating loss	(106,368)	(90,870)	(15,498)
Interest income	6,835	5,527	1,308
Net loss	$ (99,533)	$ (85,343)	$ (14,190)

Collaboration Revenue

Collaboration revenue increased $12.7 million to $43.1 million during the year ended December 31, 2019, as compared to $30.4 million during the year ended December 31, 2018. The increase in collaboration revenue during the year ended December 31, 2019 is primarily caused by a $8.5 million increase related to the Novartis Amendment to the 2014 Novartis Agreement, for which we received a one-time payment of $10.0 million in December 2018. Additionally, collaboration revenue increased $4.5 million in 2019 over 2018 due to increased research and development services related to our ATTR program, increasing to $12.0 million during 2019 as compared with $7.5 million in 2018. Regeneron was obligated to fund 50% of the research and development costs for the ATTR program.

Research and Development

Research and development expenses increased $19.3 million to $108.4 million during the year ended December 31, 2019, as compared to $89.1 million during the year ended December 31, 2018. This increase is primarily related to an increase in research and development expenses of $10.3 million related to laboratory supplies, research materials and contract services for the further advancement of our pipeline and platform costs; an increase in personnel-related costs of $4.7 million, driven by our growth in headcount; and an increase related to IP license and acquisition costs of $1.7 million. These increases were offset in part by a $2.0 million decrease in stock-based compensation due primarily to some of our earlier grants being fully vested.

During 2020, we expect research and development expenses to increase as we continue to grow our research and development team and begin clinical development.

General and Administrative

General and administrative expenses increased $8.9 million to $41.1 million during the year ended December 31, 2019, as compared to $32.2 million during the year ended December 31, 2018. This increase was primarily related to an increase of $5.5 million in legal fees, which were principally related to IP matters, an increase of $1.7 million in personnel-related costs and $0.5 million in professional services.

Interest Income

Interest income increased by $1.3 million to $6.8 million during the year ended December 31, 2019 as compared to $5.5 million during the year ended December 31, 2018. This increase was primarily caused by an increase in our average invested balance.

Liquidity and Capital Resources

Since our inception through December 31, 2019, we have raised an aggregate of $652.6 million to fund our operations, of which $154.5 million was through our collaboration agreements, $170.5 million was from our initial public offering and concurrent private placements, $141.0 million was from a follow-on public offering, $101.6 million was from at-the-market offerings and $85.0 million was from the sale of convertible preferred stock.

As of December 31, 2019, we had $284.5 million in cash, cash equivalents and marketable securities.

We are eligible to earn a significant amount of milestone payments and royalties, in each case, on a per-product basis under our collaboration with Novartis and on a per-target basis under our collaboration with Regeneron, subject to the provisions of our agreements with each of them. Our ability to earn these payments and the timing of achieving these milestones is dependent upon the outcome of our or their research and development activities and is uncertain at this time. Our rights to payments under our collaboration agreements are our only committed external source of funds.

At-the-Market Offering Programs

On October 12, 2018, we filed a Shelf Registration Statement on Form S-3 (the "2018 Shelf") with the SEC in relation to the registration of common stock, preferred stock, warrants and units of any combination thereof for the purposes of selling, from time to time, our common stock, convertible securities or other equity securities in one or more offerings. We also simultaneously entered into an Open Market Sale Agreement (the "2018 Sales Agreement") with Jefferies LLC (the "Sales Agent"), to provide for the offering, issuance and sale of up to an aggregate amount of $100.0 million of our common stock from time to time in "at-the-market" offerings under the 2018 Shelf and subject to the limitations thereof. We have paid the Sales Agent cash commissions of 3.0% of the gross proceeds of sales of common stock under the 2018 Sales Agreement. In November 2018, we issued 1,659,300 shares of our common stock at $18.00 per share in accordance with the 2018 Sales Agreement for aggregate net proceeds of $28.5 million, after payment of cash commissions to the Sales Agent and approximately $0.4 million related to legal, accounting and other fees in connection with the sale. During the twelve months ended December 31, 2019, we issued an additional 4,231,348 shares of our common stock, in a series of sales, at an average price of $16.57 per share, in accordance with the 2018 Sales Agreement, for aggregate net proceeds of $67.8 million, after payment of cash commissions to the Sales Agent and approximately $0.2 million related to legal, accounting and other fees in connection with the sales. As of December 31, 2019, there were no shares of common stock eligible for sale under the 2018 Sales Agreement.

On August 23, 2019, we filed a Registration Statement on Form S-3, as amended (the "2019 Shelf") with the SEC in relation to the registration of common stock, preferred stock, warrants and units of any combination thereof. We also simultaneously entered into an Open Market Sale Agreement (the "2019 Sales Agreement") with the Sales Agent, to provide for the offering, issuance and sale by us of up to an aggregate amount of $150.0 million of our common stock from time to time in "at-the-market" offerings under the 2019 Shelf and subject to the limitations thereof. We agreed to pay to the Sales Agent cash commissions of 3.0% of the gross proceeds of sales of common stock under the 2019 Sales Agreement. During the year ended December 31, 2019, we issued 287,231 shares of our common stock, in a series of sales, at an average price of $16.48 per share, in accordance with the 2019 Sales Agreement, for aggregate net proceeds of $4.4 million, after payment of cash commissions to the Sales Agent and approximately $0.2 million related to legal, accounting and other fees in connection with the sales. As of December 31, 2019, approximately $145.3 million in shares of common stock remain eligible for sale under the 2019 Sales Agreement.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, research and development contracted services, compensation and related expenses, laboratory and office facilities, research supplies, legal and regulatory expenses, patent prosecution filing and maintenance costs for our licensed IP and general overhead costs. During 2020, we expect our expenses to increase compared to prior periods in connection with our ongoing activities, as we continue to grow our research and development team and begin clinical development.

Because our research programs are still in preclinical development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts necessary to successfully complete the development and commercialization of any future product candidates or whether, or when, we may achieve profitability. Until such time as we can generate substantial product revenues, if ever, we expect to finance our ongoing cash needs through equity financings and collaboration arrangements. We receive cost reimbursements from Regeneron for the ATTR program. Additionally, we are eligible to earn milestone payments and royalties, in each case, on a per-product basis under our collaboration with Novartis and on a per-target basis under our collaboration with Regeneron, subject to the provisions of our agreements with each of them. Except for these sources of funding, we will not have any committed external source of liquidity. To the extent that we raise additional capital through the future sale of equity, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing stockholders. If we raise additional funds through collaboration arrangements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Outlook

Based on our research and development plans and our expectations related to the progress of our programs, we expect that our cash, cash equivalents and marketable securities as of December 31, 2019, as well as research and cost reimbursement funding from Regeneron, will enable us to fund our ongoing operating expenses and capital expenditure requirements at least to the end of 2021, excluding any potential milestone payments or extension fees that could be earned and distributed under the collaboration agreements with Regeneron and Novartis or any strategic use of capital not currently in the base case planning assumptions. We have based this estimate on current assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect.

Our ability to generate revenue and achieve profitability depends significantly on our success in many areas, including: developing our delivery technologies and our CRISPR/Cas9 technology platform; selecting appropriate product candidates to develop; completing research and preclinical and clinical development of selected product candidates; obtaining regulatory approvals and marketing authorizations for product candidates for which we complete clinical trials; developing a sustainable and scalable manufacturing process for product candidates; launching and commercializing product candidates for which we obtain regulatory approvals and marketing authorizations, either directly or with a collaborator or distributor; obtaining market acceptance of our product candidates; addressing any competing technological and market developments; negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter; maintaining good relationships with our collaborators and licensors; maintaining, protecting, and expanding our portfolio of IP rights, including patents, trade secrets, and know-how; and attracting, hiring, and retaining qualified personnel.

Cash Flows

The following is a summary of cash flows for the years ended December 31, 2019 and 2018:

	Year Ended December 31,	
	2019	2018
	(In millions)	
Net cash used in operating activities	$ (103.2)	$ (61.3)
Net cash provided by (used in) investing activities	25.2	(260.8)
Net cash provided by financing activities	76.4	40.2

Net cash used in operating activities

Net cash used in operating activities of $103.2 million and $61.3 million during the years ended December 31, 2019 and 2018, respectively, primarily reflect increased spend in our research and development and general and administrative activities, offset in part by the receipt of $18.9 million and $29.4 million in payments from our collaboration partners, respectively, during those periods.

Net cash provided by (used in) investing activities

During the year ended December 31, 2019, our investing activities provided net cash of $25.2 million. During the year ended December 31, 2018, our investing activities used net cash of $260.8 million. The increase in the year ended December 31, 2019 is primarily due to an increase of $32.0 million from marketable securities activity during the period, as $329.0 million in marketable securities matured and $297.0 million in marketable securities were purchased. This increase was offset in part by the use of $6.8 million related to purchases of property and equipment as we continue to grow our operations. The decrease in the year ended December 31, 2018 was primarily for the purchase of marketable securities amounting to $254.6 million as a result of a change to our investment policy in September 2018, allowing for investment in marketable securities. This change in policy resulted in $255.2 million being shown as marketable securities on our December 31, 2018 balance sheet. The remainder of the decrease in the year ended December 31, 2018 related to purchases of property and equipment as we grew our operations and build out of our office and laboratory facilities after moving to our new corporate office in December 2016.

Net cash provided by financing activities

Net cash provided by financing activities of $76.4 million during the year ended December 31, 2019 includes $72.3 million in net proceeds from at-the-market offerings, $3.1 million in cash received from the exercise of stock options and $1.1 million in cash received from the issuance of shares through our employee stock purchase plan. Net cash provided by financing activities of $40.2 million during the year ended December 31, 2018 includes $28.5 million in net proceeds from an at-the-market offering, $10.7 million in cash received from the exercise of stock options and $1.0 million in cash received from the issuance of shares through our employee stock purchase plan.

Contractual Obligations

The following summarizes our contractual obligations as of December 31, 2019:

	Payments Due by Period				
	Total	Less than 1 Year	1 to 3 Years	3 to 5 Years	More than 5 Years
			(In millions)		
Property leases	$ 21.0	$ 7.1	$ 12.1	$ 1.8	$ -
Other arrangements	7.4	6.2	1.2	-	-

The amounts reported for property leases represent future minimum lease payments under non-cancelable operating leases in effect as of December 31, 2019. The minimum lease payments do not include common area maintenance charges or real estate taxes.

Other arrangements represent agreements with certain vendors for supply manufacturing, preclinical research studies and other services and products that are enforceable and legally binding.

Other contractual obligations

The contractual obligations table does not include any potential future pass-through milestone payments or royalty payments we may be required to make under our existing license agreements due to the uncertainty of the occurrence of the events requiring payment under those agreements. The table also excludes our obligation to pay 30.0% of Caribou's patent prosecution filing and maintenance costs for licensed IP as such costs cannot be reliably estimated until incurred.

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based upon our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the U.S. The preparation of these consolidated financial statements requires us to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities as of the date of the balance sheets and the reported amounts of collaboration revenue and expenses during the reporting periods. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances at the time such estimates are made. Actual results and outcomes may differ materially from our estimates, judgments and assumptions. We periodically review our estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates are reflected in the consolidated financial statements prospectively from the date of the change in estimate.

We define our critical accounting policies as those accounting principles generally accepted in the U.S. that require the most significant estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations as well as the specific manner in which we apply those principles. We believe the critical accounting policies used in the preparation of our consolidated financial statements which require significant estimates and judgments are as follows:

Revenue Recognition

We adopted Accounting Standards Update ("ASU") 2014-09, *Revenue from Contracts with Customers (Topic 606),* and its related amendments (collectively known as "ASC 606") on January 1, 2018 using the modified retrospective method. The reported results for 2019 and 2018 reflect the application of ASC 606 guidance, while the reported results for 2017 were prepared under the guidance of ASC 605, *Revenue Recognition* ("ASC 605" or "legacy GAAP"). The adoption of ASC 606 represented a change in accounting principle that more closely aligns revenue recognition with the delivery of our goods and services and provides financial statement readers with enhanced disclosures.

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

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

The transaction price is determined based on the consideration to which we will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration, we estimate the amount of variable consideration that should be included in the transaction price utilizing either the expected value method or the most likely amount method, depending on the nature of the variable consideration. Variable consideration is included in the transaction price if, in our judgment, it is probable that a significant future reversal of cumulative revenue under the contract will not occur. Any estimates, including the effect of the constraint on variable consideration, are evaluated at each reporting period for any changes. Determining the transaction price requires significant judgment, which is discussed in further detail for each of our collaboration agreements in Note 9. In addition, none of our contracts as of December 31, 2019 contained a significant financing component.

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price to each performance obligation on a relative standalone selling price basis unless the transaction price is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct service that forms part of a single performance obligation. The consideration to be received is allocated among the separate performance obligations based on relative standalone selling prices. We typically determine standalone selling prices using an adjusted market assessment approach model.

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

As of December 31, 2019, our only revenue recognized is related to collaboration agreements with third parties which are either within the scope of ASC 606, under which we license certain rights to our product candidates to third parties, or within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808") if it involves a joint operating activity pursuant to which we are an active participant and are exposed to significant risks and rewards with respect to the arrangement. As discussed in further detail in Note 9, we enter into out-licensing agreements which are within the scope of ASC 606, under which we license certain rights to our product candidates to third parties. The terms of these arrangements typically include payment to us of one or more of the following: nonrefundable, upfront fees; development, regulatory, and commercial milestone payments; research and development funding payments; and royalties on the net sales of licensed products. Each of these payments results in collaboration revenues, except for revenues from royalties on the net sales of licensed products, which are classified as royalty revenues. For arrangements within the scope of ASC 808, the terms of these arrangements typically include payments received or made under the cost sharing provisions which are recognized as a component of revenues in the consolidated statements of operations and comprehensive loss.

Licenses of intellectual property: If the license to our IP is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenues from consideration allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the licenses. For licenses that are combined with other promises, we utilize judgment to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue.

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

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

We receive payments from our customers based on billing schedules established in each contract. Our contract liabilities consist of deferred revenue. Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until we satisfy our obligations under these arrangements.

We also consider the nature and contractual terms of an arrangement and assess whether the arrangement involves a joint operating activity pursuant to which we are an active participant and exposed to significant risks and rewards with respect to the arrangement. If we are an active participant and exposed to the significant risks and rewards with respect to the arrangement, we account for the arrangement under ASC 808. Based on this consideration, we account for our Co/Co agreement with Regeneron under ASC 808. Because ASC 808 does not provide recognition and measurement guidance for collaborative arrangements, we have analogized to ASC 606.

Costs to obtain and fulfill a contract

We did not incur any expenses to obtain collaboration agreements and costs to fulfill those contracts do not generate or enhance our resources. As such, no costs to obtain or fulfill a contract have been capitalized in any period.

Equity-Based Compensation

We measure employee equity-based compensation based on the grant date fair value of the equity awards using the Black-Scholes option pricing model. Equity-based compensation expense is recognized on a straight-line basis over the requisite service period of the awards and is adjusted for pre-vesting forfeitures in the period in which the forfeitures occur. For equity awards that have a performance condition, we recognize compensation expense based on our assessment of the probability that the performance condition will be achieved.

We classify equity-based compensation expense in our consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's salary and related costs are classified or in which the award recipient's service payments are classified.

Recent Accounting Pronouncements

Please read Note 2 to our consolidated financial statements included in Part IV, Item 15, "Notes to Consolidated Financial Statements," of this annual report on Form 10-K for a description of recent accounting pronouncements applicable to our business.

Off-Balance Sheet Arrangements

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

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

The market risk inherent in our financial instruments and in our financial position represents the potential loss arising from adverse changes in interest rates. As of December 31, 2019, we had cash equivalents and marketable securities of $274.2 million consisting of interest-bearing money market accounts, commercial paper, corporate and financial institution debt securities, U.S. Treasury securities and asset-backed securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are primarily in marketable securities. Due to the short-term duration of our investment portfolios and the low risk profile of our investments, we do not believe an immediate change of 100 basis points, or one percentage point, would have a material effect on the fair market value of our investment portfolio. Declines in interest rates, however, would reduce future investment income.

We do not have any foreign currency or derivative financial instruments. Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our results of operations during the year ended December 31, 2019.

Item 8. Financial Statements and Supplementary Data

The information required by this item is presented at the end of this report beginning on page F-1.

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

The Company has established disclosure controls and procedures designed to ensure that information required to be disclosed in the reports that the Company files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms and is accumulated and communicated to management, including the principal executive officer (our Chief Executive Officer) and principal financial officer (our Chief Financial Officer), to allow timely decisions regarding required disclosure.

Our management, under the supervision and with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of the end of the period covered by this Annual Report on Form 10-K. Management recognizes that any disclosure controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives. Our disclosure controls and procedures have been designed to provide reasonable assurance of achieving their objectives. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2019.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

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

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2019. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in *Internal Control—Integrated Framework* (2013 framework) ("COSO"). Based on its assessment, management believes that, as of December 31, 2019, our internal control over financial reporting is effective based on those criteria.

Deloitte & Touche LLP, our independent registered public accounting firm, has issued an attestation report on the effectiveness of our internal control over financial reporting, which is included below.

Changes in Internal Controls over Financial Reporting

No change in the Company's internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2019 that has materially affected, or is reasonably likely to materially affect, the Company's internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Intellia Therapeutics, Inc.

Opinion on Internal Control over Financial Reporting

We have audited the internal control over financial reporting of Intellia Therapeutics, Inc. and subsidiary (the "Company") as of December 31, 2019, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by COSO.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated financial statements as of and for the year ended December 31, 2019, of the Company and our report dated February 27, 2020, expressed an unqualified opinion on those financial statements and included an explanatory paragraph regarding the Company's adoption of Accounting Standards Codification Topic 842, *Leases*, on January 1, 2019.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

/s/ Deloitte & Touche LLP

Boston, Massachusetts
February 27, 2020

Item 9B. Other Information

None.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K and is incorporated by reference from our definitive proxy statement relating to our 2020 annual meeting of stockholders, pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, also referred to in this Annual Report on Form 10-K as our 2020 Proxy Statement, which we expect to file with the SEC no later than April 29, 2020.

Item 10. Directors, Executive Officers and Corporate Governance

Information regarding our directors, including the audit committee and audit committee financial experts, and executive officers and compliance with Section 16(a) of the Exchange Act will be included in our 2020 Proxy Statement and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics for all of our directors, officers and employees as required by Nasdaq governance rules and as defined by applicable SEC rules. Stockholders may locate a copy of our Code of Business Conduct and Ethics on our website at www.intelliatx.com or request a copy without charge from:

Intellia Therapeutics, Inc.
Attention: Investor Relations
40 Erie Street, Suite 130
Cambridge, MA 02139

We will post to our website any amendments to the Code of Business Conduct and Ethics, and any waivers that are required to be disclosed by the rules of either the SEC or Nasdaq.

Item 11. Executive Compensation

The information required by this item regarding executive compensation will be included in our 2020 Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item regarding security ownership of certain beneficial owners and management and securities authorized for issuance under equity compensation plans will be included in our 2020 Proxy Statement and is incorporated herein by reference.

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

The information required by this item regarding certain relationships and related transactions and director independence will be included in our 2020 Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item regarding principal accounting fees and services will be included in our 2020 Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits, Financial Statement Schedules

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

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

   Report of Independent Registered Public Accounting Firm

   Consolidated Balance Sheets

   Consolidated Statements of Operations and Comprehensive Loss

   Consolidated Statements of Stockholders' Equity

   Consolidated Statements of Cash Flows

   Notes to Consolidated Financial Statements

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

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

Item 16. Form 10-K Summary

The Company has elected not to include summary information.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Intellia Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Intellia Therapeutics, Inc. and subsidiary (the "Company") as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows, for each of the three years in the period ended December 31, 2019, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with accounting principles generally accepted in the United States of America.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 27, 2020, expressed an unqualified opinion on the Company's internal control over financial reporting.

Change in Accounting Principle

As discussed in Note 2 to the financial statements, effective January 1, 2019, the Company adopted FASB Accounting Standards Codification Topic 842, *Leases*, using the modified retrospective approach and utilizing the effective date as its date of adoption.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current-period audit of the financial statements that was communicated or required to be communicated to the audit committee and that (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Revenue Recognition — Collaboration Arrangements – Refer to Notes 2 and 9 to the financial statements.

Critical Audit Matter Description

The Company recognizes collaboration revenue on license and collaboration agreements as they fulfill their performance obligations and transfer control of goods and services to the customer. Management uses judgement in determining when the performance obligation is complete, either over time or at a point in time. For performance obligations related to services that are required to be recognized over time, there is significant judgment involved in determining the most appropriate measure of progress towards satisfaction of each performance obligation. As of December 31, 2019, collaboration revenue was $43.1 million, of which $31.1 million was recognized over time.

We identified revenue recognized over time as a critical audit matter because of the judgments necessary for management to determine an appropriate measure of progress. This required an increased extent of audit effort and a high degree of auditor judgment when performing procedures to audit the estimated measure of progress when revenue is recognized over time.

How the Critical Audit Matter Was Addressed in the Audit

Our audit procedures related to the estimated measure of progress included the following, among others:

- We tested the effectiveness of controls over the Company's revenue recognition process, including controls over management's estimated measure of progress when revenue is recognized over time.
- We selected collaboration agreements and performed the following:
    - Evaluated the appropriateness and consistency of the methods and assumptions used by management to develop the estimated measure of progress and performed corroborating inquiries with the Company's project managers and scientists.
    - Tested the mathematical accuracy of management's calculation of revenue recognized over time.

/s/ Deloitte & Touche LLP
Boston, Massachusetts
February 27, 2020

We have served as the Company's auditor since 2015.

INTELLIA THERAPEUTICS, INC.
CONSOLIDATED BALANCE SHEETS
(Amounts in thousands except share and per share data)

	December 31, 2019	December 31, 2018
ASSETS		
Current Assets:		
Cash and cash equivalents	$ 57,226	$ 58,856
Marketable securities	222,500	255,203
Accounts receivable	4,620	7,547
Prepaid expenses and other current assets	5,135	3,371
Total current assets	289,481	324,977
Marketable securities - noncurrent	4,746	-
Property and equipment, net	17,996	17,061
Operating lease right-of-use assets	19,137	-
Other assets	2,920	5,277
Total Assets	$ 334,280	$ 347,315
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current Liabilities:		
Accounts payable	$ 3,941	$ 2,708
Accrued expenses	13,273	10,742
Current portion of operating lease liability	5,745	-
Current portion of deferred revenue	12,674	27,122
Total current liabilities	35,633	40,572
Deferred revenue, net of current portion	16,136	28,810
Long-term operating lease liability	12,630	-
Other long-term liabilities	-	13
Commitments and contingencies (Note 8)		
Stockholders' Equity:		
Common stock, $0.0001 par value; 120,000,000 shares authorized; 50,198,044 and 45,224,480 shares issued and outstanding at December 31, 2019 and 2018, respectively	5	5
Additional paid-in capital	570,493	478,968
Accumulated other comprehensive income (loss)	261	(28)
Accumulated deficit	(300,878)	(201,025)
Total stockholders' equity	269,881	277,920
Total Liabilities and Stockholders' Equity	$ 334,280	$ 347,315

See notes to consolidated financial statements.

INTELLIA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(Amounts in thousands except per share data)

	Year Ended December 31,		
	2019	2018	2017
Collaboration revenue	$ 43,103	$ 30,434	$ 26,117
Operating expenses:			
Research and development	108,413	89,115	67,647
General and administrative	41,058	32,189	28,025
Total operating expenses	149,471	121,304	95,672
Operating loss	(106,368)	(90,870)	(69,555)
Interest income	6,835	5,527	2,012
Net loss	$ (99,533)	$ (85,343)	$ (67,543)
Net loss per share, basic and diluted	$ (2.11)	$ (1.98)	$ (1.88)
Weighted average shares outstanding, basic and diluted	47,247	43,069	36,006
Other comprehensive income (loss):			
Unrealized gain (loss) on marketable securities	289	(28)	-
Comprehensive loss	$ (99,244)	$ (85,371)	$ (67,543)

See notes to consolidated financial statements.

INTELLIA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(Amounts in thousands, except share data)

	Common Shares	Common Amount	Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Income	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2016	36,018,540	$ 4	$ 263,403	$ -	$ (53,570)	$ 209,837
Issuance of common stock	6,250,000	-	141,000	-	-	141,000
Exercise of stock options	141,759	-	1,156	-	-	1,156
Issuance of shares under employee stock purchase plan	64,786	-	825	-	-	825
Equity-based compensation	(90,462)	-	15,322	-	-	15,322
Net loss	-	-	-	-	(67,543)	(67,543)
Balance at December 31, 2017	42,384,623	4	421,706	-	(121,113)	300,597
Retroactive adjustment to beginning accumulated deficit for adoption of ASU 2014-09	-	-	-	-	5,431	5,431
Issuance of common stock through at-the-market offerings, net of issuance costs of $424	1,659,300	1	28,547	-	-	28,548
Exercise of stock options	1,142,944	-	10,651	-	-	10,651
Issuance of shares under employee stock purchase plan	68,865	-	1,018	-	-	1,018
Equity-based compensation	(31,252)	-	17,046	-	-	17,046
Other comprehensive loss	-	-	-	(28)	-	(28)
Net loss	-	-	-	-	(85,343)	(85,343)
Balance at December 31, 2018	45,224,480	5	478,968	(28)	(201,025)	277,920
Retroactive adjustment to beginning accumulated deficit for adoption of ASC 842	-	-	-	-	(320)	(320)
Issuance of common stock through at-the-market offerings, net of issuance costs of $363	4,518,579	-	72,256	-	-	72,256
Exercise of stock options	364,404	-	3,086	-	-	3,086
Issuance of shares under employee stock purchase plan	90,581	-	1,092	-	-	1,092
Equity-based compensation	-	-	15,091	-	-	15,091
Other comprehensive income	-	-	-	289	-	289
Net loss	-	-	-	-	(99,533)	(99,533)
Balance at December 31, 2019	50,198,044	$ 5	$ 570,493	$ 261	$ (300,878)	$ 269,881

INTELLIA THERAPEUTICS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(Amounts in thousands)

	Year Ended December 31,		
	2019	**2018**	**2017**
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net loss	$ (99,533)	$ (85,343)	$ (67,543)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	5,587	4,464	2,994
Loss on disposal of property and equipment	1	75	166
Equity-based compensation	15,091	17,046	15,322
Accretion of investment discounts	(3,725)	(676)	-
Changes in operating assets and liabilities:			
Accounts receivable	2,927	2,924	(4,017)
Prepaid expenses and other current assets	(1,763)	310	(1,893)
Operating right-of-use assets	5,728	-	-
Other assets	153	1,022	902
Accounts payable	1,880	232	(488)
Accrued expenses	2,310	2,780	2,394
Deferred revenue	(27,122)	(3,936)	(12,988)
Operating lease liabilities	(4,774)	-	-
Other long-term liabilities	-	(155)	(125)
Net cash used in operating activities	(103,240)	(61,257)	(65,276)
CASH FLOWS FROM INVESTING ACTIVITIES:			
Purchases of property and equipment	(6,794)	(6,358)	(10,091)
Proceeds from sale of property and equipment	-	131	-
Purchases of marketable securities	(297,030)	(254,555)	-
Maturities of marketable securities	329,000	-	-
Net cash provided by (used in) investing activities	25,176	(260,782)	(10,091)
CASH FLOWS FROM FINANCING ACTIVITIES:			
Proceeds from common stock offerings, net of offering costs	72,256	28,547	141,000
Proceeds from options exercised	3,086	10,652	1,156
Issuance of shares through employee stock purchase plan	1,092	1,018	825
Net cash provided by financing activities	76,434	40,217	142,981
Net (decrease) increase in cash and cash equivalents	(1,630)	(281,822)	67,614
Cash and cash equivalents, beginning of period	58,856	340,678	273,064
Cash and cash equivalents, end of period	$ 57,226	$ 58,856	$ 340,678
SUPPLEMENTAL DISCLOSURES OF CASH FLOW INFORMATION:			
Purchases of property and equipment unpaid at period end	$ 800	$ 1,071	$ 805
Right-of-use assets acquired under operating leases	2,554	-	-

See notes to consolidated financial statements.

1. The Company

Intellia Therapeutics, Inc. ("Intellia" or the "Company") is a leading genome editing company focused on developing curative therapeutics utilizing a biological tool known as CRISPR/Cas9, which stands for Clustered, Regularly Interspaced Short Palindromic Repeats ("CRISPR")/CRISPR associated 9 ("Cas9"). This is a technology for genome editing, the process of altering selected sequences of genomic deoxyribonucleic acid ("DNA"). The Company believes that CRISPR/Cas9 technology has the potential to transform medicine by editing disease-associated genes with a single treatment course, and that it can also be used to create novel engineered cell therapies that can replace a patient's diseased cells or effectively target various cancers and autoimmune diseases. The Company is leveraging its leading scientific expertise, clinical development experience and intellectual property ("IP") position to unlock a broad set of therapeutic applications for CRISPR/Cas9 genome editing and to develop a potential new class of therapeutic products.

The Company was founded and commenced active operations in mid-2014. The Company will require substantial additional capital to fund its research and development. The Company is subject to risks and uncertainties common to early stage companies in the biotechnology industry, including, but not limited to, development by competitors of more advanced or effective therapies, dependence on key executives, protection of and dependence on proprietary technology, compliance with government regulations and ability to secure additional capital to fund operations. Programs currently moving into development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel and infrastructure and extensive compliance-reporting capabilities. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

2. Summary of Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Intellia Therapeutics, Inc. and its wholly owned, controlled subsidiary, Intellia Securities Corp. All intercompany balances and transactions have been eliminated in consolidation. Comprehensive loss is comprised of net loss and gain/loss on marketable securities.

Use of Estimates

The preparation of the Company's consolidated financial statements in accordance with accounting principles generally accepted ("GAAP") in the United States of America ("U.S.") requires management to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities as of the date of the consolidated financial statements and the reported amounts of collaboration revenue and expenses during the reporting periods. Significant estimates in these consolidated financial statements have been made in connection with the calculation of revenues, research and development expenses and equity-based compensation expense. The Company bases its estimates on historical experience and various other assumptions that management believes to be reasonable. Actual results could differ from those estimates. Changes in estimates are reflected in reported results in the period in which they become known.

Fair Value Measurements

The Company's financial instruments include cash equivalents, marketable securities, accounts receivable, accounts payable and accrued expenses. The Company's financial assets, which include cash equivalents and marketable securities, have been initially valued at the transaction price, and subsequently revalued at the end of each reporting period, utilizing third-party pricing services or other observable market data. The pricing services utilize industry standard valuation models and observable market inputs to determine value.

Refer to Note 4 for further information regarding the Company's fair value measurements.

Other financial instruments, including accounts receivable, accounts payable and accrued expenses, are carried at cost, which approximate fair value due to the short duration and term to maturity.

Cash Equivalents

The Company considers all highly liquid investments with maturities of three months or less when purchased to be cash equivalents. As of December 31, 2019 and 2018, cash equivalents consisted of interest-bearing money market accounts.

Marketable Securities

The Company's marketable securities are accounted for as available-for-sale and recorded at fair value with the related unrealized gains and losses included in accumulated other comprehensive income (loss), a component of stockholders' equity. Refer to Note 3 for further information regarding the Company's marketable securities.

Concentrations of Credit Risk

The Company's cash, cash equivalents and marketable securities may potentially be subject to concentrations of credit risk. The Company generally maintains balances in various accounts in excess of federally insured limits with financial institutions that management believes to be of high credit quality.

Accounts receivable represent amounts due from collaboration partners. The Company monitors economic conditions to identify facts or circumstances that may indicate that any of its accounts receivable are at risk of collection. As of December 31, 2019 and 2018, the Company's two collaboration partners, Regeneron Pharmaceuticals, Inc. ("Regeneron") and Novartis Institutes for BioMedical Research, Inc. ("Novartis"), accounted for all of the Company's accounts receivable.

Property and Equipment

The Company records property and equipment at cost and recognizes depreciation and amortization using the straight-line method over the following estimated useful lives of the respective assets:

Asset Category	Useful Life
Laboratory equipment	5 years
Office furniture and equipment	5 years
Computer software	3 years
Computer equipment	3 years
Leasehold improvements	5 years or term of respective lease, if shorter

Expenditures for repairs and maintenance of assets are expensed as incurred. Upon retirement or sale, the cost of assets disposed and the corresponding accumulated depreciation are removed from the related accounts and any resulting gain or loss is reflected in the results of operations.

Impairment of Long-Lived Assets

The Company tests long-lived assets to be held and used, including property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying amount of assets or asset groups may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets.

Evaluation of recoverability of the asset or asset group is based on an estimate of undiscounted future cash flows resulting from the use of the asset or asset group and its eventual disposition. In the event that such cash flows are not expected to be sufficient to recover the carrying amount of the asset or asset group, the assets are written down to their estimated fair values. The impairment loss would be based on the excess of the carrying value of the impaired asset over its fair value, determined based on discounted cash flows. To date, the Company has not recorded any material impairment losses on long-lived assets.

Income Taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences attributable to differences between carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax reporting purposes and for operating loss and tax credit carryforwards. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes.

The Company's deferred tax assets and liabilities are measured using enacted tax rates expected to apply in the years in which these temporary differences are expected to be recovered or settled. A valuation allowance is recorded to reduce deferred tax assets if it is determined that it is more likely than not that all or a portion of the deferred tax asset will not be realized. The Company considers many factors when assessing the likelihood of future realization of deferred tax assets, including recent earnings results, expectations of future taxable income, carryforward periods available and other relevant factors. The Company records changes in the required valuation allowance in the period that the determination is made.

The Company assesses its income tax positions and records tax benefits for all years subject to examination based upon management's evaluation of the facts, circumstances and information available as of the reporting date. For those tax positions where it is more likely than not that a tax benefit will be sustained, the Company records the largest amount of tax benefit with a greater than 50% likelihood of being realized upon ultimate settlement with a taxing authority having full knowledge of all relevant information. For those income tax positions where it is not more likely than not that a tax benefit will be sustained, the Company does not recognize a tax benefit in the financial statements. The Company records interest and penalties related to uncertain tax positions, if applicable, as a component of income tax expense.

Revenue Recognition

The Company adopted Accounting Standards Update ("ASU") 2014-09, *Revenue from Contracts with Customers (Topic 606)* and its related amendments (collectively known as Accounting Standard Codification ("ASC") 606 "ASC 606") on January 1, 2018 using the modified retrospective method. The reported results for 2019 and 2018 reflect the application of ASC 606 guidance while the reported results for 2017 were prepared under the guidance of ASC 605, *Revenue Recognition* ("ASC 605" or "legacy GAAP"). The adoption of ASC 606 represented a change in accounting principle that more closely aligns revenue recognition with the delivery of the Company's goods and services and provides financial statement readers with enhanced disclosures.

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

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

The transaction price is determined based on the consideration to which the Company will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration, the Company estimates the amount of variable consideration that should be included in the transaction price utilizing either the expected value method or the most likely amount method, depending on the nature of the variable consideration. Variable consideration is included in the transaction price if, in the Company's judgment, it is probable that a significant future reversal of cumulative revenue under the contract will not occur. Any estimates, including the effect of the constraint on variable consideration, are evaluated at each reporting period for any changes. Determining the transaction price requires significant judgment, which is discussed in further detail for each of the Company's collaboration agreements in Note 9. In addition, none of the Company's contracts as of December 31, 2019 contained a significant financing component.

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price to each performance obligation on a relative standalone selling price basis unless the transaction price is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct service that forms part of a single performance obligation. The consideration to be received is allocated among the separate performance obligations based on relative standalone selling prices. The Company typically determines standalone selling prices using an adjusted market assessment approach model.

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

As of December 31, 2019, the Company's only revenue recognized is related to collaboration agreements with third parties which are either within the scope of ASC 606, under which the Company licenses certain rights to its product candidates to third parties, or within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808") if it involves a joint operating activity pursuant to which the Company is an active participant and is exposed to significant risks and rewards with respect to the arrangement. For the collaboration arrangements under the scope of ASC 606, as discussed in further detail in Note 9, the terms of these arrangements typically include payment to the Company of one or more of the following: nonrefundable, upfront fees; development, regulatory, and commercial milestone payments; research and development funding payments; and royalties on the net sales of licensed products. Each of these payments results in collaboration revenues, except for revenues from royalties on the net sales of licensed products, which are classified as royalty revenues. For arrangements within the scope of ASC 808, the terms of these arrangements typically include payments received or made under the cost sharing provisions which are recognized as a component of revenues in the consolidated statements of operations and comprehensive loss.

Licenses of intellectual property: If the license to the Company's IP is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenues from consideration allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the licenses. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue.

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

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

The Company receives payments from its customers based on billing schedules established in each contract. The Company's contract liabilities consist of deferred revenue. Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until the Company satisfies its obligations under these arrangements.

The Company also considers the nature and contractual terms of an arrangement and assesses whether the arrangement involves a joint operating activity pursuant to which the Company is an active participant and is exposed to significant risks and rewards with respect to the arrangement. If the Company is an active participant and is exposed to the significant risks and rewards with respect to the arrangement, the Company accounts for the arrangement under ASC 808. Based on this consideration, the Company accounts for its Co-Development and Co-Promotion ("Co/Co") Agreement with Regeneron under ASC 808. Because ASC 808 does not provide recognition and measurement guidance for collaborative arrangements, the Company has analogized to ASC 606. Refer to Note 9 for additional information regarding the Company's collaboration agreements.

Research and Development Expenses

Research and development costs are expensed as incurred. Research and development expenses consist of salaries, equity-based compensation and benefits of employees, lab supplies and materials, facilities expenses, overhead expenses, fees paid to subcontractors and contract research organizations and other external expenses.

The Company records payments made for research and development services prior to the services being rendered as prepaid expense on the consolidated balance sheet and expenses them as the services are provided. Contracts for multi-year research and development services are recorded on a straight-line basis over each annual contractual period based on the total contractual fee when the services rendered are expected to be substantially equivalent over the term of the arrangement. The cost of obtaining licenses for certain technology or IP is recorded to research and development expense when incurred if the licensed technology or IP has not yet reached technological feasibility and has no alternative future use.

Equity-Based Compensation

The Company measures employee equity-based compensation based on the grant date fair value of the equity awards using the Black-Scholes option pricing model. Equity-based compensation expense is recognized on a straight-line basis over the requisite service period of the awards and is adjusted for pre-vesting forfeitures in the period in which the forfeitures occur. For equity awards that have a performance condition, the Company recognizes compensation expense based on its assessment of the probability that the performance condition will be achieved.

The Company classifies equity-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's salary and related costs are classified or in which the award recipient's service payments are classified.

(Loss) Earnings per Share

The Company calculates basic (loss) earnings per share by dividing (loss) income by the weighted average number of common shares outstanding. The Company computes diluted (loss) earnings per share after giving consideration to the dilutive effect of stock options and unvested restricted stock that are outstanding during the period, except where such non-participating securities would be anti-dilutive.

Segment Information

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's one business segment is the development of genome editing-based therapies. All of the Company's assets are held in the U.S. and all of the Company's revenue has been generated in the U.S.

Recent Accounting Pronouncements – Adopted

Leases

Effective January 1, 2019, the Company adopted ASC 842, *Leases* ("ASC 842"), using the required modified retrospective approach and utilizing the effective date as its date of initial application. As a result, prior periods are presented in accordance with the previous guidance in ASC Topic 840, *Leases*.

At the inception of an arrangement, the Company determines whether an arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Most leases with a term greater than one year are recognized on the consolidated balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company has elected not to recognize leases with terms of 12 months or less on the consolidated balance sheets. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty that the Company will renew. The Company monitors its plans to renew its material leases on a quarterly basis.

Operating lease liabilities and their corresponding right-of-use assets are recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in the Company's leases is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. In its transition to ASC 842, the Company utilized the remaining lease term of its leases in determining the appropriate incremental borrowing rates.

In accordance with ASC 842, components of a lease should be allocated between lease components (e.g., land, building, etc.) and non-lease components (e.g., common area maintenance, consumables, etc.). The fixed and in-substance fixed contract consideration must be allocated based on the respective relative fair values to the lease components and non-lease components.

Although separation of lease and non-lease components is otherwise required, an expedient is available whereby the entity may account for each lease component and related non-lease component together as a single lease component. For new and amended leases for office and laboratory space beginning in 2019 and after, the Company has elected to account for the lease and non-lease components together as a single lease component for all underlying assets and allocate all of the contract consideration to the lease component only.

ASC 842 provides several optional practical expedients in transition. The Company elected the package of practical expedients which allows the Company to not reassess its existing conclusions on lease identification, classification, and initial direct costs. Further, the Company elected the hindsight practical expedient and utilized the short-term lease exemption for all leases with an original term of 12 months or less, for purposes of applying the recognition and measurement requirements of the new standard. The Company also elected the practical expedient which allows it to not separate lease and non-lease components for all its current office and laboratory leases.

The adoption of the new standard on January 1, 2019 resulted in the recognition of operating lease liabilities of $20.6 million, and right-of-use assets of $22.3 million on the Company's consolidated balance sheet relating to its leases. Further, an adjustment to retained earnings of $0.3 million was recognized due to the use of hindsight being applied in updating the lease term for the Company's property leases. The adoption of the standard did not have a material effect on the Company's consolidated statements of operations and comprehensive loss or consolidated statements of cash flows.

Refer to Note 10 for the Company's current lease commitments.

In June 2018, the Financial Accounting Standards Board ("FASB") issued ASU 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*, which simplified the accounting for share-based payments to nonemployees by aligning it with the accounting for share-based payments to employees, with certain exceptions. The Company's adoption of the new standard on January 1, 2019 did not have a material effect on the Company's consolidated financial statements.

Recent Accounting Pronouncements – Issued but not yet adopted

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes* ("ASU 2019-12"). The amendments in ASU 2019-12 are effective for fiscal years beginning after December 15, 2020, including interim periods therein. Early adoption of the standard is permitted. The Company does not anticipate that the adoption of ASU 2019-12 will have a material effect on the Company's consolidated financial statements.

In August 2018, the FASB issued ASU 2018-13, *Fair Value Measurement (Topic 820): Disclosure Framework – Changes to the Disclosure Requirements for Fair Value Measurement* ("ASU 2018-13"). The new standard removes certain disclosures, modifies certain disclosures and adds additional disclosures related to fair value measurement. The new standard was effective beginning January 1, 2020 and early adoption is permitted. The Company does not anticipate that the adoption of ASU 2018-13 will have a material effect on its disclosures upon adoption.

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"). The standard changes how credit losses are measured for most financial assets and certain other instruments. For trade and other receivables, the standard requires the use of a new forward-looking "expected credit loss" model that generally will result in the earlier recognition of allowances for losses. For available-for-sale debt securities with unrealized losses, the standard now requires allowances to be recorded instead of reducing the amortized cost of the investment. The new standard also requires new disclosures and was effective beginning January 1, 2020. With certain exceptions, the guidance is applied using a modified retrospective approach by reflecting adjustments through a cumulative-effect impact to retained earnings as of the beginning of the fiscal year of adoption. The Company does not anticipate that the adoption of ASU 2016-13 will have a material effect on the Company's consolidated financial statements.

3. Marketable Securities

The following table summarizes the Company's available-for-sale marketable securities as of December 31, 2019 and 2018 at net book value:

	December 31, 2019			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(In thousands)			
Marketable securities:				
U.S. Treasury securities	$ 159,361	$ 142	$ (1)	$ 159,502
Financial institution debt securities	40,173	105	-	40,278
Corporate debt securities	18,966	1	-	18,967
Other asset-backed securities	8,485	14	-	8,499
Total	$ 226,985	$ 262	$ (1)	$ 227,246

	December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
	(In thousands)			
Marketable securities:				
U.S. Treasury securities	$ 165,959	$ 2	$ (13)	$ 165,948
Financial institution debt securities	65,436	1	(17)	65,420
Corporate debt securities	23,836	-	(1)	23,835
Total	$ 255,231	$ 3	$ (31)	$ 255,203

The amortized cost of available-for-sale securities is adjusted for amortization of premiums and accretion of discounts to maturity. At December 31, 2019 and 2018, the balance in the Company's accumulated other comprehensive income (loss) was composed of activity related to the Company's available-for-sale marketable securities. There were no material realized gains or losses in the years ended December 31, 2019, 2018 or 2017 and, as a result, the Company did not reclassify any amounts out of accumulated other comprehensive income (loss) during these periods. The Company did not have any securities in a material unrealized loss position at December 31, 2019 or 2018.

The Company's available-for-sale securities that are classified as short term marketable securities in the consolidated balance sheet mature within one year or less as of the balance sheet date. Available-for-sale securities that are classified as noncurrent in the consolidated balance sheet mature after one year but within five years from the balance sheet date. At December 31, 2019 and 2018, the Company did not hold any investments that matured beyond five years.

4. Fair Value Measurements

The Company classifies fair value-based measurements using a three-level hierarchy that prioritizes the inputs used to measure fair value. This hierarchy requires entities to maximize the use of observable inputs and minimize the use of unobservable inputs. The three levels of inputs used to measure fair value are as follows: Level 1, quoted market prices in active markets for identical assets or liabilities; Level 2, observable inputs other than quoted market prices included in Level 1, such as quoted market prices for markets that are not active or other inputs that are observable or can be corroborated by observable market data; and Level 3, unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities, including certain pricing models, discounted cash flow methodologies and similar techniques that use significant unobservable inputs.

As of December 31, 2019 and 2018, the Company's financial assets recognized at fair value on a recurring basis consisted of the following:

	Fair Value as of December 31, 2019			
	Total	Level 1	Level 2	Level 3
	(In thousands)			
Cash equivalents	$ 46,917	$ 46,917	$ -	$ -
Marketable securities:				
U.S. Treasury securities	159,502	159,502	-	-
Financial institution debt securities	40,278	-	40,278	-
Corporate debt securities	18,967	-	18,967	-
Other asset-backed securities	8,499	-	8,499	-
Total marketable securities	227,246	159,502	67,744	-
Total	$ 274,163	$ 206,419	$ 67,744	$ -

	Fair Value as of December 31, 2018			
	Total	Level 1	Level 2	Level 3
	(In thousands)			
Cash equivalents	$ 45,986	$ 45,986	$ -	$ -
Marketable securities:				
U.S. Treasury securities	165,948	165,948	-	-
Financial institution debt securities	65,420	-	65,420	-
Corporate debt securities	23,835	-	23,835	-
Total marketable securities	255,203	165,948	89,255	-
Total	$ 301,189	$ 211,934	$ 89,255	$ -

The Company's financial assets, which include cash equivalents and marketable securities, have been initially valued at the transaction price, and subsequently revalued at the end of each reporting period, utilizing third-party pricing services or other observable market data. The pricing services utilize industry standard valuation models and observable market inputs to determine value. After completing its validation procedures, the Company did not adjust or override any fair value measurements provided by the pricing services as of December 31, 2019 or 2018.

5. Property and Equipment, Net

Property and equipment, net consisted of the following:

	December 31,	
	2019	2018
	(in thousands)	
Laboratory equipment	$ 27,199	$ 22,453
Office furniture and equipment	1,121	960
Computer equipment	1,051	929
Leasehold improvements	1,474	898
Computer software	1,019	433
Total property and equipment	31,864	25,673
Less: accumulated depreciation and amortization	(13,868)	(8,612)
Property and equipment, net	$ 17,996	$ 17,061

Depreciation and amortization expense was $5.6 million, $4.5 million and $3.0 million for the years ended December 31, 2019, 2018 and 2017, respectively.

6. Accrued Expenses

Accrued expenses consisted of the following:

	December 31, 2019	December 31, 2018
	(In thousands)	
Employee compensation and benefits	$ 6,311	$ 6,175
Accrued research and development	4,208	2,328
Accrued legal and professional expenses	1,563	1,633
Accrued other	1,191	606
Total accrued expenses	$ 13,273	$ 10,742

7. Income Taxes

The Company did not record net income tax benefits for the operating losses incurred during the periods presented due to the uncertainty of realizing a tax benefit from those losses. Accordingly, any benefit recorded related to these deferred tax assets was offset by a valuation allowance reflecting management's conclusion that realization of those assets was not more likely than not.

A reconciliation of the federal statutory income tax rate and the Company's effective income tax rate is as follows:

	Year Ended December 31,		
	2019	2018	2017
Federal statutory income tax rate	(21.0)%	(21.0)%	(34.0)%
State income taxes	(8.9)	(8.6)	(6.9)
Research and development tax credits	(5.1)	(4.7)	(3.4)
Stock-based compensation	1.2	(0.6)	3.6
Change in U.S. tax rate	-	-	18.7
Change in valuation allowance	33.8	34.9	22.0
Effective income tax rate	-%	-%	-%

The Company's net deferred tax assets (liabilities) consisted of the following:

	December 31,	
	2019	2018
	(in thousands)	
Deferred tax assets:		
Intangibles, including acquired in-process research and development	$ 1,091	$ 1,201
Capitalized start-up costs	421	463
Net operating loss carryforwards	63,245	34,234
Research and development credit carryforwards	19,417	11,766
Operating lease liability	5,008	-
Deferred revenue	7,843	12,199
Equity-based compensation	7,092	4,064
Accruals and allowances	1,245	1,359
Gross deferred tax assets	105,362	65,286
Deferred tax asset valuation allowance	(98,513)	(64,046)
Total deferred tax assets	6,849	1,240
Deferred tax liabilities:		
Fixed assets	(1,633)	(1,240)
Operating lease right-of-use assets	(5,216)	-
Total deferred tax liabilities	(6,849)	(1,240)
Net deferred tax asset (liability)	$ -	$ -

As of December 31, 2019, the Company had federal and state net operating loss carryforwards of $229.9 million and $236.8 million, respectively. As of December 31, 2019, approximately $193.0 million of the Company's federal net operating loss carryforward can be carried forward indefinitely while the remaining federal net operating loss of $36.9 million begins to expire in 2034. As of December 31, 2019, the Company had federal and state research and development and other credit carryforwards of approximately $12.6 million and $8.7 million, which begin to expire in 2035 and 2031, respectively.

The Company evaluated the expected realizability of its net deferred tax assets and determined that there was significant negative evidence due to its net operating loss position and insufficient positive evidence to support the realizability of these net deferred tax assets. The Company concluded it is more likely than not that its net deferred tax assets would not be realized in the future; therefore, the Company has provided a full valuation allowance against its net deferred tax asset balance as of December 31, 2019 and 2018. The valuation allowance increased by $34.5 million in 2019, $28.7 million in 2018 and $14.8 million in 2017.

Utilization of the net operating loss and research and development credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended, due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of net operating loss and research and development credit carryforwards that can be utilized annually to offset future taxable income and tax expense, respectively. The Company has not yet conducted a study to assess whether a change of control, as defined in Section 382, has occurred or whether there have been multiple changes in control since inception.

As of December 31, 2019, the Company had not identified any unrecognized tax benefits. The Company files income tax returns in the U.S. federal tax jurisdiction and Massachusetts and various other state tax jurisdictions. The Company is subject to examination by the Internal Revenue Service and Massachusetts taxing authorities. The returns in these jurisdictions since inception remain open for examination; however, there are currently no pending tax examinations.

8. Commitments and Contingencies

In July 2014, the Company licensed from Caribou Biosciences, Inc. ("Caribou") certain IP (the "Caribou License") and entered into an arrangement under which Caribou provided research and development services. On October 17, 2018, the Company initiated an arbitration proceeding against Caribou, asserting that Caribou is violating the terms and conditions of the Caribou License, as well as other contractual and legal rights, by using and seeking to license to third parties two patent families (described in, for instance, PCT No. PCT/US2016/015145 and PCT No. PCT/US2016/064860, and related patents and applications) relating to specific structural or chemical modifications of guide RNAs ("gRNA"s), that were purportedly invented or controlled by Caribou, in the Company's exclusive human therapeutic field. Caribou asserted that the two families of IP are outside the scope of the Company's field of use under the license rights granted to the Company under the Caribou License. In accordance with the Caribou License, the Company submitted a demand for arbitration seeking among other relief a declaration that the disputed IP was included within the scope of its field of use under the Caribou License.

On September 26, 2019, the Company announced that the arbitration panel issued an interim award concluding that both the structural and chemical gRNAs modification technologies were exclusively licensed to the Company by Caribou pursuant to the Caribou License. After concluding that the chemical modification technology was within the scope of the Company's exclusive license from Caribou, the arbitration panel nevertheless noted that its decision could delay or otherwise adversely impact the development of these modified gRNAs as human therapeutics. It also noted that the Company currently is not using these modified gRNAs in any of its active programs. Thus, solely with respect to the particular modified gRNAs, the arbitration panel stated that it will declare that Caribou has an equitable "leaseback," which it described as exclusive, perpetual and worldwide (the "Caribou Award"). The panel instructed the parties to negotiate the terms of the Caribou Award, including Caribou's future payments to the Company for the same, but the parties' negotiations reached an impasse.

On February 6, 2020, after considering additional submissions from the parties, the panel clarified that the Caribou Award is limited to one particular on-going Caribou program, which seeks to develop a chimeric antigen receptor ("CAR") T ("CAR-T") product directed at CD19. The panel instructed the parties to seek to negotiate terms based on this scope. Accordingly, the Caribou Award will be subject to terms, including Caribou's future payments to the Company to be negotiated by the parties or, if unsuccessful, adjudicated in additional arbitration or judicial proceedings.

Pursuant to the September 2019 interim award, the Caribou Award by the panel does not include the structural guide modifications IP at issue in the arbitration, any other IP exclusively licensed or sublicensed by Caribou to the Company under the Caribou License (including but not limited to the foundational CRISPR/Cas9 IP co-owned by the Regents of the University of California, University of Vienna and Dr. Emmanuelle Charpentier), or any other of the Company's IP.

Upon, and subject to the terms of, a final award, which will follow further arbitration or legal proceedings and potential additional negotiations between the parties, Caribou could be able to use the modified gRNAs at issue for CAR-T cell human therapeutics directed at CD19. Either the Company or Caribou may challenge the arbitration panel's decisions under limited circumstances.

Other than with regards to the technologies in dispute, the interim award has no effect on the Company's rights or Caribou's obligations under the Caribou License.

License Agreements

The Company is party to license agreements, which include contingent payments. These payments will become payable if and when certain development, regulatory and commercial milestones are achieved. As of December 31, 2019, the satisfaction and timing of the contingent payments is uncertain and not reasonably estimable.

9. Collaborations

To accelerate the development and commercialization of CRISPR/Cas9-based products in multiple therapeutic areas, the Company has formed, and intends to seek other opportunities to form, strategic alliances with collaborators who can augment its leadership in CRISPR/Cas9 therapeutic development. As of December 31, 2019 and December 31, 2018, the Company's accounts receivable and contract liabilities were primarily related to the Company's collaborations with Novartis and Regeneron.

The following table presents changes in the Company's accounts receivable and contract liabilities during the years ended December 31, 2019 and 2018 (in thousands):

	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
Year Ended December 31, 2019				
Accounts receivable	$ 7,547	$ 15,999	$ (18,926)	$ 4,620
Contract liabilities:				
Deferred revenue	$ 55,932	$ 4,000	$ (31,122)	$ 28,810

	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
Year Ended December 31, 2018				
Accounts receivable	$ 10,471	$ 16,498	$ (19,422)	$ 7,547
Contract liabilities:				
Deferred revenue	$ 59,868	$ 19,000	$ (22,936)	$ 55,932

During the years ended December 31, 2019 and 2018, the Company recognized the following revenues as a result of changes in the contract liability balance (in thousands):

Revenue recognized in the period from:	Year Ended December 31, 2019	Year Ended December 31, 2018
Amounts included in the contract liability at the beginning of the period	$ 27,122	$ 22,936

Costs to obtain and fulfill a contract

The Company did not incur any expenses to obtain collaboration agreements and costs to fulfill those contracts do not generate or enhance resources of the Company. As such, no costs to obtain or fulfill a contract have been capitalized in any period.

Novartis Institutes for BioMedical Research, Inc.

In December 2014, the Company entered into a strategic collaboration agreement with Novartis (the "2014 Novartis Agreement"), primarily focused on the research of new *ex vivo* CRISPR/Cas9-edited therapies using CAR-T cells and hematopoietic stem cells ("HSCs"). The agreement was amended in December 2018 to also include research on ocular stem cells ("OSCs"). In December 2019, per the terms of the 2014 Novartis Agreement, the research term ended, although the 2014 Novartis Agreement remains in effect. As provided in the agreement, Novartis has selected various CAR-T, HSC and OSC targets for continued development, for which the Company will be eligible to receive milestone and royalty payments in the future.

Agreement Structure. Under the 2014 Novartis Agreement, the parties agreed to engage in collaborative research activities using the Company's CRISPR/CAS9 platform to identify and research therapeutic, prophylactic and palliative products and services relating to the following applications: a) *ex vivo* HSCs and b) *ex vivo* CAR-T cells. In addition, in the last two years of the collaboration term, Novartis was permitted to engage in research and development of a limited number of *in vivo* targets using the Company's platform.

Scope of Collaboration. During the five-year research term, the parties researched potential therapeutic, prophylactic and palliative *ex vivo* applications of CRISPR/Cas9 technology in HSCs and CAR-T cells. Research expenses incurred by the Company in support of the collaboration were reimbursed by Novartis.

HSC Program. The Company and Novartis agreed to collaborate exclusively with each other during the research term to conduct research on *ex vivo* applications of CRISPR/Cas9 technology for HSC targets under a research plan agreed upon by both parties. At the end of the research term in December 2019, this exclusive HSC research collaboration ended. Within the *ex vivo* HSC therapeutic space, Novartis obtained exclusive rights to research and develop human therapeutics for a limited number of HSC targets, which were selected by Novartis in a series of selection windows.

During the research term, the Company had the right to choose a limited number of HSC targets for its exclusive development and commercialization per the specified selection schedule. Following these selections by Novartis and the Company, Novartis had the right to research an additional limited number of non-selected HSC targets on a non-exclusive basis, but Novartis did not exercise this right. Because the research term has ended, the parties can no longer select additional exclusive HSC targets, and Novartis has an exclusive license to research, develop and commercialize human therapeutic products directed to its selected HSC targets. Novartis assumed sole responsibility for developing and commercializing human therapeutic products for the HSC targets it selected arising from the Company's collaboration and is solely responsible for the costs and expenses of developing, manufacturing and commercializing its HSC products. To maintain its exclusive license on a target-by-target basis, Novartis is required to use commercially reasonable efforts to research, develop and commercialize at least one HSC product directed to each of their selected HSC targets. In 2019, Novartis announced that it had completed investigational new drug ("IND")-enabling studies in support of a potential IND on a program targeting sickle cell disease that leveraged the Company's CRISPR/Cas 9 technology. The Company is entitled to receive a $5.0 million payment related to this regulatory milestone upon filing the IND.

CAR-T Program. The Company and Novartis also agreed to collaborate exclusively with each other during the research term on research directed to applying CRISPR/Cas9 technology to CAR-T cell targets under a research plan agreed upon by both parties. At the end of the research term in December 2019, this exclusive research collaboration ended. Under the 2014 Novartis Agreement, Novartis assumed sole responsibility for developing human therapeutic products for the limited number of CAR targets it selected arising from its collaboration with the Company and is solely responsible for the costs and expenses of developing, manufacturing and commercializing its selected targets. Novartis has an exclusive license to research, develop and commercialize CAR products directed to its selected CAR-T cell targets. To maintain its exclusive license on a target-by-target basis, Novartis is required to use commercially reasonable efforts to research, develop and commercialize at least one CAR-T cell product directed to each of its selected CAR targets.

Governance. The parties formed HSC and CAR-T cell steering committees with responsibility for oversight of these respective research programs and approval of the associated research plans. Beginning in December 2018, the HSC steering committee also became responsible for the OSC program (see the section below entitled "*2018 Amendment to the Agreement")*. These steering committees in turn were overseen by a joint steering committee and comprised an equal number of representatives from each party. The steering committees terminated upon completion of the research term in December 2019.

Financial Terms. The Company received an upfront technology access payment from Novartis of $10.0 million in January 2015 and was 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. As of December 31, 2019, the Company has received $20.0 million in technology access fees and $19.0 million in research payments related to these programs. In addition, for each Novartis product under the collaboration (whether HSC or CAR-T cell product, and beginning as of December 2018, an OSC product), subject to certain conditions, the Company may be eligible to receive (i) up to $30.3 million in development milestones, including for the filing of an IND 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 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.

Equity Investments. Additionally, at the inception of the arrangement at which time the Company was a privately held company, Novartis invested $9.0 million to purchase the Company's Class A-1 and Class A-2 Preferred Units (the "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.

License Grant to Novartis. In the 2014 Novartis Agreement, the Company granted to Novartis a license to its CRISPR/Cas9 platform technology, including a sublicense to certain platform rights licensed from Caribou, that is exclusive in the *ex vivo* 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 CRISPR-edited products directed to such targets.

License Grant to Intellia. In the 2014 Novartis Agreement, prior to the Novartis Amendment described below, Novartis granted the Company a non-exclusive license to its IP covering a small molecule for HSC expansion and to its lipid nanoparticle ("LNP") platform technology to research, develop and commercialize HSC and *in vivo* genome editing products, respectively, in the 2014 Novartis Agreement.

Intellectual Property. IP that the Company develops within the collaboration related to the Company's CRISPR/Cas9 platform will be owned solely by the Company, while all other IP developed within the collaboration, including IP covering products arising from the collaboration, will be jointly owned by the Company and Novartis.

2018 Amendment to the Agreement

In December 2018, the Company entered into an amendment to this agreement with Novartis (the "Novartis Amendment") which expanded the scope of the 2014 Novartis Agreement to include the *ex vivo* development of CRISPR/Cas9-based cell therapies using limbal stem cells, a type of OSC, primarily against gene targets selected by Novartis in exchange for a one-time payment of $10.0 million which the Company received in December 2018. The governance, license rights and development responsibilities, as well as milestones and royalties, associated with any OSC program and product follow those for the HSC programs and products. Because the research term has ended, as with the HSC programs, the parties' exclusive research collaboration for limbal stem cells has ended, and Novartis has an exclusive license to research, develop and commercialize OSC products directed to a limited number of OSC targets. As part of the Novartis Amendment, Intellia rights to Novartis' LNP technology were expanded to include use in all genome editing applications in both *in vivo* and *ex vivo* settings.

Term and Termination. The term of the 2014 Novartis 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 the Company 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) ten years after the first commercial sale of such product in such country. The Company may terminate the agreement if Novartis or its affiliates institute a patent challenge against its IP rights, and all improvements thereto, licensed to Novartis under the agreement. Novartis may terminate the agreement, without cause, upon 90 days' written notice to the Company subject to certain conditions and continuing obligations. Either party may terminate the agreement in the event of the other party's uncured material breach or bankruptcy - or insolvency-related events.

Accounting Analysis. The Company concluded that the 2014 Novartis Agreement and the Novartis Amendment are subject to ASC 606 and assessed its accounting for them accordingly. The Company evaluated the promised goods and services under the 2014 Novartis Agreement and determined that it had two performance obligations: (1) a combined performance obligation representing a series of distinct goods and services including the licenses to research, develop and commercialize HSC and LSC products and their associated research activities and the licenses to research, develop and commercialize CAR-T cell products and their associated research activities; and (2) the Preferred Units.

The Company determined that the transaction price of the 2014 Novartis Agreement was $59.0 million consisting of the following consideration: (1) the upfront technology access payment of $10.0 million; (2) the additional technology access fees of $20.0 million; (3) the Company's estimate of variable consideration of $20.0 million related to the quarterly research payments; and (4) the payment for the Preferred Units of $9.0 million. None of the clinical or regulatory milestones were included in the transaction price, as all milestone amounts were fully constrained. As part of its evaluation of the constraint, the Company considered numerous factors, including that receipt of the milestones is outside the control of the Company and contingent upon future regulatory progress and the licensee's efforts. Any consideration related to sales-based milestones and royalties will be recognized when the related sales occur as they were determined to relate predominantly to the licenses granted to Novartis and therefore have also been excluded from the transaction price. The Company will re-evaluate the transaction price in each reporting period and when events whose outcomes are resolved or other changes in circumstances occur.

The Company first allocated $11.6 million of the transaction price to the Preferred Units to record the Preferred Units purchased by Novartis at fair value. The Company then allocated the remaining $47.4 million of the transaction price to the remaining combined performance obligation of the licenses and associated research activities for HSC and CAR-T cell products. Revenue allocated to the combined performance obligation of the licenses and associated research activities for HSC and CAR-T cell products is being recognized using a time elapsed inputs method over a period of five years, which, in management's judgment, is the best measure of progress towards satisfying the performance obligation as this method provides the most faithful depiction of the entity's performance in transferring control of the goods and services promised to Novartis and represents the Company's best estimate of the period of the obligation.

The Company determined that there is only one combined performance obligation identified under the Novartis Amendment, representing a series of distinct goods and services including the licenses to research, develop and commercialize products using LSCs and their associated research and development services related to the research, development and commercialization of products using LSCs, and allocated the $10.0 million transaction price accordingly. Revenue allocated to this performance obligation is being recognized using a time elapsed inputs method over a period of one year, which, in management's judgment, is the best measure of progress towards satisfying the performance obligation as this method provides the most faithful depiction of the entity's performance in transferring control of the goods and services promised to Novartis and represents the Company's best estimate of the period of the obligation.

Revenue Recognition: Collaboration Revenue. Through December 31, 2019, excluding amounts allocated to Novartis' purchase of the Company's Preferred Units, the Company had recorded a total of $57.4 million in cash and accounts receivable under the 2014 Novartis Agreement and the Novartis Amendment. Through December 31, 2019, the Company has recognized $57.4 million of collaboration revenue, including $18.5 million in the year ended December 31, 2019, $10.3 million in the year ended December 31, 2018, and $9.3 million in the year ended December 31, 2017, in the consolidated statements of operations and comprehensive loss related to the 2014 Novartis Agreement and the Novartis Amendment. As of December 31, 2019, the aggregate transaction price had been recognized in full.

As of the periods ended December 31, 2019 and 2018, the Company had accounts receivable of $1.0 million and $6.0 million, respectively, related to this agreement. As of December 31, 2019, the Company had no deferred revenue related to this agreement. As of December 31, 2018, the Company had deferred revenue of $14.5 million related to this agreement.

Regeneron Pharmaceuticals, Inc.

In April 2016, the Company entered into a license and collaboration agreement with Regeneron (the "Regeneron Agreement").

Agreement Structure. The Regeneron Agreement has two principal components: i) a product development component under which the parties will research, develop and commercialize CRISPR/Cas-based therapeutic products primarily focused on genome editing in the liver, and ii) a technology collaboration component, pursuant to which the Company and Regeneron will engage in research and development activities aimed at discovering and developing novel technologies and improvements to CRISPR/Cas technology to enhance the Company's genome editing platform. Under this agreement, the Company also may access the Regeneron Genetics Center and proprietary mouse models to be provided by Regeneron for a limited number of the Company's liver programs.

Scope of Collaboration. Under the terms of the six-year collaboration, Regeneron may obtain exclusive rights for up to ten targets to be chosen by Regeneron during the collaboration term, subject to a target selection process and various adjustments and limitations set forth in the agreement. Of these ten total targets, Regeneron may select up to five non-liver targets, while the remaining targets must be focused in the liver. Certain non-liver targets from the Company's ongoing and planned research at the time, as well as any targets included in another of the Company's collaborations, are excluded from this collaboration. At the inception of the agreement, Regeneron selected the first of its ten targets, transthyretin amyloidosis ("ATTR"), which is subject to a Co/Co agreement between the Company and Regeneron, the general terms and conditions for which were outlined within the Regeneron Agreement.

Research Collaboration. 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. The Company will assist Regeneron with the preliminary evaluation of its selected liver targets, and Regeneron will be responsible for preclinical research and conducting clinical development, manufacturing and commercialization of products directed to each of its exclusive targets. The Company 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 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.

Reserved Liver Targets. The Company retains the exclusive right to solely develop products via CRISPR/Cas genome editing directed against certain specified genetic targets. During the collaboration term and subject to a target selection process, the Company has the right to choose additional liver targets for its own development using commercially reasonable efforts. Certain targets that either the Company or Regeneron select during the term may be subject to further Co/Co agreements at the Company or Regeneron's option, as applicable, which either can exercise pursuant to defined conditions.

Governance. Under the Regeneron Agreement, the parties formed a joint steering committee, which is responsible for setting research objectives and overseeing the general strategies and research and development activities undertaken by the parties. Additionally, under the Co/Co agreement directed to ATTR (the "ATTR Co/Co"), the parties formed a Joint Development and Commercialization Committee ("JDCC") to oversee all profit share products under the Co/Co agreement as discussed below. The JDCC has responsibility for overseeing the development, manufacture, regulatory matters, and commercialization (including pricing and reimbursement) of ATTR, as the first profit share product under the Regeneron agreement.

Financial Terms. The Company received a nonrefundable upfront payment of $75.0 million. In addition, on Regeneron programs that are not subject to Co/Co agreements the Company may be eligible to earn, on a per-licensed target basis, (i) up to $25.0 million in development milestones, including for the dosing of the first patient in each of Phase I, Phase II and Phase III clinical trials, (ii) up to $110.0 million in regulatory milestones, including for the acceptance of a regulatory filing in the U.S., and for obtaining regulatory approval in the U.S. and in certain other identified countries, and (iii) up to $185.0 million in sales-based milestone payments. The Company is 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 incorporate the Company's existing low- to mid-single-digit royalty obligations under a license agreement with Caribou.

Equity Investments. In connection with this collaboration, Regeneron purchased $50.0 million of the Company's common stock in a private placement under a Stock Purchase Agreement concurrent with the Company's initial public offering ("IPO").

Term and Termination. The research collaboration term ends in April 2022, except that Regeneron may make a one-time payment of $25.0 million to extend the term for an additional two-year period. The Regeneron 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. The Company may terminate the Regeneron Agreement on a target-by-target basis if Regeneron or any of its affiliates institutes a patent challenge against the Company's CRISPR/Cas or certain other background patent rights or 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 the Company, either in its entirety or on a target-by-target basis, in which event, certain rights in the terminated targets and associated IP revert to the Company, as described in the agreement. Following such termination, the Company may owe Regeneron royalties, in certain circumstances, up to mid-single digits on any terminated targets that the Company subsequently commercializes 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 Regeneron Agreement either in its entirety or with respect to the research collaboration or one or more of the targets selected by Regeneron, in the event of the other party's uncured material breach.

Co-Development and Co-Promotion Agreement. In July 2018, the Company and Regeneron finalized the form of the Co/Co agreement that will be used as the basis for each Co/Co agreement directed to a target. Simultaneously, the Company and Regeneron executed the Co/Co agreement directed to the first collaboration target, ATTR, for which the Company is the clinical and commercial Lead Party (see below) and Regeneron is the Participating Party (see below).

Co-Development and Co-Promotion: Agreement Structure Under the Regeneron Agreement, Regeneron has the right to exercise at least five options to enter into a Co/Co agreement for the Company's liver targets (other than the Company's reserved liver targets), while the Company may exercise at least one option to enter into a Co/Co agreement for Regeneron's liver targets, the exact number of options being subject to certain conditions of the target selection process. Each option to enter into a Co/Co agreement must be exercised (or forfeited) once a target reaches a defined preclinical stage. Within 15 days of exercising the option, the party exercising the option must pay $1.5 million to the other party as compensation for prior work. The ATTR program was exempted from this payment. One party will be the "Lead Party" and the other party the "Participating Party". The Lead Party shall have control and primary responsibility for the development, manufacturing, regulatory and commercial activities. The Participating Party shall have the right to consult on these activities through its participation on the JDCC and will have the right to co-fund development and commercialization activities in exchange for a share of profits. In general, under each Co/Co agreement, the parties will share equally in worldwide development costs and profits of any future products. Prior to reaching a specific development milestone, the Participating Party may elect to reduce its share of worldwide development costs and profits by 50%. Pursuant to the ATTR Co/Co, on December 13, 2019, Regeneron informed the Company that it would exercise its rights under the ATTR Co/Co agreement to modify its share of worldwide development costs and profits from 50% to 25%, effective six months after its notice.

Co-Development and Co-Promotion: Termination. Either party may terminate by providing 180 days written notice. If the Company terminates, the product becomes a Regeneron product, and is subject to all future milestone and royalty payment obligations under the Regeneron Agreement. If Regeneron terminates and has contributed at least $5 million in development costs under the Co/Co agreement, the Company will pay low- to mid-single digit royalties on the net sales of the product, depending on co-funding percentage, stage at termination and, if any, Regeneron IP incorporated into the product.

Accounting Analysis. The Company determined that the Regeneron Agreement is within the scope of ASC 606. The Company evaluated the promised goods and services under the Regeneron Agreement and determined that the Regeneron Agreement included three performance obligations: (1) a combined performance obligation including the licenses to targets and the associated research activities and evaluation plans; (2) a combined performance obligation including the technology collaboration and associated research activities; and (3) the common stock.

The Company also concluded that the ATTR Co/Co agreement meets the definition of a collaborative arrangement per ASC 808, which is outside of the scope of ASC 606. Since ASC 808 does not provide recognition and measurement guidance for collaborative arrangements, the Company has analogized to ASC 606. As such, the Company classifies payments received or made under the cost sharing provisions of the ATTR Co/Co agreement as a component of revenues in the consolidated statements of operations and comprehensive loss.

Under the Regeneron Agreement, the Company determined that the transaction price was $125.0 million, consisting of the following consideration: (1) the nonrefundable upfront payment of $75.0 million; and (2) the payment for the common stock of $50.0 million. None of the clinical or regulatory milestones were included in the transaction price, as all milestone amounts were fully constrained. As part its evaluation of the constraint, the Company considered numerous factors, including that receipt of the milestones is outside the control of the Company and contingent upon success in future regulatory progress and the licensee's efforts. Any consideration related to sales-based milestones and royalties will be recognized when the related sales occur as they were determined to relate predominantly to the licenses granted to Regeneron and therefore have also been excluded from the transaction price. The Company will re-evaluate the transaction price in each reporting period and when events whose outcome are resolved or other changes in circumstances occur.

The Company first allocated $50.0 million of the transaction price to the common stock. The common stock was sold at its standalone selling price and the Company concluded that the total discount inherent in the arrangement is entirely attributable to the combined performance obligation including the licenses to targets and associated research activities and evaluation plans and the combined performance obligation including the technology collaboration and associated research activities. As such, the remaining $75.0 million of the transaction price was allocated to the combined performance obligation including the licenses to targets and associated research activities and evaluation plans and the combined performance obligation including the technology collaboration and associated research activities on a relative standalone selling price basis. The Company estimated the standalone selling price of each combined performance obligation by taking into consideration internal estimates of research and development personnel needed to perform the research and development services, estimates of expected cash outflows to third parties for services and supplies, selling prices of comparable transactions and typical gross profit margins. As a result of this evaluation, the Company allocated $63.8 million to the combined performance obligation including the licenses to targets and associated research activities and evaluation plans and $11.2 million to the combined performance obligation including the technology collaboration and associated research activities. The $63.8 million allocated to the combined performance obligation including the licenses to targets and associated research activities and evaluation plans is being recognized using a time elapsed inputs method over a period of six years, which, in management's judgment, is the best measure of progress towards satisfying the performance obligation as this method provides the most faithful depiction of the entity's performance in transferring control of the goods and services promised to Regeneron and represents the Company's best estimate of the period of the obligation. The $11.2 million allocated to the combined performance obligation including the technology collaboration and associated research activities is being recognized using a time elapsed inputs method over a period beginning with the inception of the technology collaboration in September 2016 through the end of the arrangement, which, in management's judgment, is the best measure of progress towards satisfying the performance obligation as this method provides the most faithful depiction of the entity's performance in transferring control of the goods and services promised to Regeneron and represents the Company's best estimate of the period of the obligation.

Revenue Recognition: Collaboration Revenue. Through December 31, 2019, excluding the amounts allocated to Regeneron's purchase of the Company's common stock, the Company recorded a $75.0 million upfront payment and $24.1 million for research and development services under the Regeneron Agreement. As of December 31, 2019, there was approximately $28.8 million of the aggregate transaction price remaining to be recognized, which will be recognized ratably through April 2022. As of December 31, 2019 and 2018, the Company had deferred revenue of $28.8 million and $41.4 million, respectively, and accounts receivable of $3.6 million and $1.5 million, respectively, related to this arrangement.

Through December 31, 2019, the Company has recognized $70.3 million, including $24.6 million, $20.1 million and $16.8 million of collaboration revenue in the years ended December 31, 2019, 2018 and 2017, respectively, in the consolidated statements of operations and comprehensive loss related to this arrangement. This includes $12.0 million, $7.5 million, and $4.1 million representing payments from Regeneron pursuant to the ATTR Co/Co agreement, which is accounted for under ASC 808.

10. Leases

In October 2014, the Company entered into an agreement to lease office and laboratory space at 130 Brookline Street in Cambridge, Massachusetts under an operating lease agreement with a term through January 2020, with an option to extend the term of the lease for an additional five-year period. In April 2019, the Company executed an amendment to the lease to extend the term of the lease for the additional five-year period, through January 2025. Upon the execution of the original lease, the Company provided a $0.3 million security deposit. The Company has recorded this security deposit in other assets on the consolidated balance sheets.

In applying the ASC 842 transition guidance, the Company retained the classification of this lease as operating and recorded a lease liability and a right-of-use asset on the ASC 842 effective date with the five-year extension included in the lease term, based on the Company's election of the hindsight practical expedient as the Company was reasonably certain to exercise this option term.

In March 2019, the Company entered into a separate agreement to sublease additional office and laboratory space at 130 Brookline Street in Cambridge, Massachusetts under an operating sublease agreement with a term through April

2021, with two options to extend the agreement by one year each, for a total option period of up to two years. Upon commencement of the lease in April 2019, the Company recognized a right-of-use asset and lease liability of approximately $1.3 million.

In January 2016, the Company entered into a ten-year agreement to lease office and laboratory space at 40 Erie Street in Cambridge, Massachusetts under an operating lease agreement, with an option to terminate the lease at the end of the sixth year and an option to extend the term of the lease for an additional three years. Upon the execution of this lease, the Company provided a $2.2 million security deposit, which has been recorded in other assets on the consolidated balance sheets.

Throughout the term of its leases, the Company is responsible for paying certain costs and expenses, in addition to the rent, as specified in the lease, including a proportionate share of applicable taxes, operating expenses and utilities. The variable portion of these costs are expensed as incurred and are disclosed as variable lease cost.

The following table contains a summary of the lease costs recognized under ASC 842 and other information pertaining to the Company's operating leases for the year ended December 31, 2019:

	Year Ended December 31, 2019 (in thousands)
Lease cost	
Operating lease cost	$ 7,431
Short-term lease cost	53
Variable lease cost	2,218
Total lease cost	$ 9,702

	Year Ended December 31, 2019 (in thousands)
Other information	
Operating cash flows used for operating leases	$ 6,476
Operating lease liabilities arising from obtaining right-of-use assets	2,554

	As of December 31, 2019
Lease term and discount rate	
Weighted average remaining lease term	3.0 years
Weighted average discount rate	9.00%

The table below reconciles the undiscounted cash flows for each of the first five years and total of the remaining years to the operating lease liabilities recorded in the consolidated balance sheet as of December 31, 2019:

	Future Operating Lease Payments
Year Ending December 31,	**(in thousands)**
2020	$ 7,113
2021	7,350
2022	4,733
2023	871
2024	871
Thereafter	73
Total lease payments	$ 21,011
Less: imputed interest	(2,636)
Total operating lease liabilities at December 31, 2019	$ 18,375

Future minimum lease payments under the Company's non-cancelable operating leases as of December 31, 2018, are as follows:

Year Ending December 31,	(In thousands)
2019	$ 5,616
2020	4,963
2021	5,507
2022	3,861
	$ 19,947

11. Equity-Based Compensation

In April 2016, the Company adopted the Amended and Restated 2015 Stock Option and Incentive Plan (the "2015 Plan"). The 2015 Plan provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. Recipients of incentive stock options and non-qualified stock options are eligible to purchase shares of the Company's common stock at an exercise price equal to the fair value of such stock on the grant date. Stock options granted under the 2015 Plan generally vest 25% on the first anniversary of the original vesting date, with the balance vesting monthly over the remaining three years, unless they contain specific performance-based vesting provisions. The maximum term of stock options granted under the 2015 Plan is ten years.

As of December 31, 2019, there were 2,655,673 shares available for future issuance. The number of shares reserved for issuance under the 2015 Plan shall be cumulatively increased by four percent of the number of shares of stock issued and outstanding on the immediately preceding December 31 or such lesser number of shares of stock as determined by the board of directors.

Equity-based compensation expense is classified in the consolidated statements of operations and comprehensive loss as follows:

	Year Ended December 31,		
	2019	2018	2017
		(In thousands)	
Research and development	$ 6,986	$ 8,994	$ 7,280
General and administrative	8,105	8,052	8,042
Total	$ 15,091	$ 17,046	$ 15,322

Restricted Stock

Restricted stock is measured at fair value based on the quoted price of the Company's common stock.

The following table summarizes the Company's restricted stock activity for the year ended December 31, 2019:

	Number of Shares	Weighted Average Grant Date Fair Value per Share
Unvested restricted stock as of December 31, 2018	109,073	$ 15.53
Granted	-	-
Vested	(37,198)	1.34
Cancelled	-	-
Unvested restricted stock as of December 31, 2019	71,875	$ 22.88

The weighted average grant date fair value of restricted stock, was $22.98 for restricted stock granted during 2018. There was no restricted stock granted in 2017 or 2019. As of December 31, 2019, there was $0.2 million of unrecognized equity-based compensation expense related to restricted stock that is expected to vest. These costs are expected to be recognized over a weighted average remaining vesting period of 1.0 year. All of the unvested restricted stock outstanding as of December 31, 2019 are performance-based restricted stock units that vest upon obtaining certain scientific, financial and regulatory milestones through 2020. These 71,875 restricted stock units are not included in computing the diluted (loss) earnings per share because the performance criteria had not been met as of the end of the reporting period.

Stock Options

The weighted average grant date fair value of options, estimated as of the grant date using the Black-Scholes option pricing model, was $9.21 per option for options granted during the year ended December 31, 2019, $15.05 per option for options granted during the year ended December 31, 2018 and $12.43 per option for options granted during the year ended December 31, 2017. The total intrinsic value (the amount by which the fair market value exceeded the exercise price) of stock options exercised during the year ended December 31, 2019, 2018 and 2017 was $2.3 million, $18.0 million, and $1.6 million, respectively. Key assumptions used to apply this pricing model were as follows:

	Year Ended December 31,		
	2019	2018	2017
Risk-free interest rate	2.1%	2.7%	2.0%
Expected life of options	6.0 years	6.0 years	6.0 years
Expected volatility of underlying stock	68.1%	87.1%	93.9%
Expected dividend yield	0.0%	0.0%	0.0%

Risk-free Interest Rate. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant with maturities approximately equal to the option's expected term.

Expected Dividend Yield. The expected dividend yield assumption is based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends.

Expected Volatility. The expected volatility was derived from a blend of average historical stock volatilities of several unrelated public companies within the Company's industry and the Company's historical volatility, both over a period equivalent to the expected term of the stock option grants.

Expected Term. The expected term represents the period that stock options awards are expected to be outstanding. For option grants that are considered to be "plain vanilla," the Company determines the expected term using the simplified method. The simplified method deems the term to be the average of the time-to-vesting and the contractual life of the options. The Company uses the simplified method because it does not have sufficient historical option exercise data to provide a reasonable basis upon which to estimate the expected term.

The Company uses the market closing price of its common stock as reported on the Nasdaq Global Select Market to determine the fair value of the shares of common stock underlying stock options. The following is a summary of stock option activity for the year ended December 31, 2019:

	Number of Options	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
			(In years)	(In thousands)
Outstanding at December 31, 2018	5,037,663	$ 15.63		
Granted	1,220,613	14.90		
Exercised	(364,404)	8.47		
Forfeited	(527,901)	18.50		
Outstanding at December 31, 2019	5,365,971	$ 15.67	7.86	$ 9,082
Exercisable at December 31, 2019	2,578,717	$ 14.11	6.92	$ 8,017

As of December 31, 2019, there was $28.2 million of unrecognized compensation cost related to stock options that have not yet vested. These costs are expected to be recognized over a weighted average remaining vesting period of 2.5 years.

Of the unvested stock options outstanding as of December 31, 2019, 213,750 are performance-based stock options that vest upon obtaining certain scientific, financial and regulatory milestones through 2020. At December 31, 2019, 188,750 performance-based options are not included in computing the diluted (loss) earnings per share because the performance criteria had not been met as of the end of the reporting period.

12. Loss Per Share

Basic and diluted loss per share was calculated as follows:

	Year Ended December 31,		
	2019	2018	2017
		(In thousands)	
Net loss	$ (99,533)	$ (85,343)	$ (67,543)
Weighted average shares outstanding, basic and diluted	47,247	43,069	36,006
Net loss per share, basic and diluted	$ (2.11)	$ (1.98)	$ (1.88)

The following common stock equivalents were excluded from the calculation of diluted loss per share in 2019, 2018 and 2017 because their inclusion would have been anti-dilutive:

	Year Ended December 31,		
	2019	2018	2017
		(In thousands)	
Unvested restricted stock	72	109	480
Stock options	5,366	5,038	4,705
	5,438	5,147	5,185

13. Stockholders' Equity

On May 11, 2016, the Company completed an IPO of its common stock, which resulted in the sale of 6,900,000 shares, including all additional shares available to cover over-allotments, at a price of $18.00 per share. In connection with the closing of the IPO, all of the Company's outstanding convertible preferred stock automatically converted to common stock at a one-for-0.6465903 ratio as of May 11, 2016, resulting in an additional 23,481,956 shares of common stock of the Company becoming outstanding. In addition, the Company issued a total of 3,055,554 shares of common stock for $55.0 million in two separate, concurrent private placements upon the closing of the IPO.

On November 1, 2017, the Company entered into an underwriting agreement related to a public offering of 6,250,000 shares of the Company's common stock, par value $0.0001 per share. The offering closed on November 6, 2017 and the Company received net proceeds of $141.0 million, after deducting underwriting discounts.

At-the-Market Offering Programs

On October 12, 2018, the Company filed a Registration Statement on Form S-3 (the "2018 Shelf") with the SEC in relation to the registration of common stock, preferred stock, warrants and units of any combination thereof for the purposes of selling, from time to time, its common stock, convertible securities or other equity securities in one or more offerings. The Company also simultaneously entered into an Open Market Sale Agreement (the "2018 Sales Agreement") with Jefferies LLC (the "Sales Agent"), to provide for the offering, issuance and sale by the Company of up to an aggregate amount of $100.0 million of its common stock from time to time in "at-the-market" offerings under the 2018 Shelf and subject to the limitations thereof. The Company paid to the Sales Agent cash commissions of 3.0% of the gross proceeds of sales of common stock under the 2018 Sales Agreement. In November 2018, the Company issued 1,659,300 shares of its common stock at $18.00 per share in accordance with the 2018 Sales Agreement for net proceeds of $28.5 million, after payment of cash commissions to the Sales Agent and approximately $0.4 million related to legal, accounting and other fees in connection with the sales. During the year ended December 31, 2019, the Company issued an additional 4,231,348 shares of its common stock, in a series of sales, at an average price of $16.57 per share, in accordance with the 2018 Sales Agreement, for aggregate net proceeds of $67.8 million, after payment of cash commissions to the Sales Agent and approximately $0.2 million related to legal, accounting and other fees in connection with the sales. As of December 31, 2019, there were no shares of common stock eligible for sale under the 2018 Sales Agreement.

On August 23, 2019, the Company filed a Registration Statement on Form S-3, as amended (the "2019 Shelf") with the SEC in relation to the registration of common stock, preferred stock, warrants and units of any combination thereof. The Company also simultaneously entered into an Open Market Sale Agreement (the "2019 Sales Agreement") with the Sales Agent, to provide for the offering, issuance and sale by the Company of up to an aggregate amount of $150.0 million of its common stock from time to time in "at-the-market" offerings under the 2019 Shelf and subject to the limitations thereof. The Company agreed to pay to the Sales Agent cash commissions of 3.0% of the gross proceeds of sales of common stock under the 2019 Sales Agreement. During the year ended December 31, 2019, the Company issued 287,231 shares of its common stock, in a series of sales, at an average price of $16.48 per share, in accordance with the 2019 Sales Agreement, for aggregate net proceeds of $4.4 million, after payment of cash commissions to the Sales Agent and approximately $0.2 million related to legal, accounting and other fees in connection with the sales. As of December 31, 2019, approximately $145.3 million in shares of common stock remain eligible for sale under the 2019 Sales Agreement.

14. Related Party Transactions

Novartis Institutes for Biomedical Research

In connection with its entry into the collaboration and license agreement and related equity transactions with Novartis, in 2015 the Company issued Novartis capital stock, and in May 2016, Novartis acquired 277,777 shares of the Company's common stock in a private placement transaction concurrent with the Company's IPO. Novartis owned less than 10% of the Company's voting interests as of December 31, 2019. Refer to Note 9 for additional information regarding this collaboration agreement.

The Company recognized collaboration revenue of $18.5 million, $10.3 million and $9.3 million in the years ended December 31, 2019, 2018 and 2017, respectively, related to this agreement. As of the periods ended December 31, 2019 and 2018, the Company had recorded accounts receivable of $1.0 million and $6.0 million related to this collaboration. There was no deferred revenue related to this collaboration at December 31, 2019. As of the period ended December 31, 2018, the Company had deferred revenue of $14.5 million related to this collaboration.

Research Material Supplier

In the ordinary course of business, the Company may purchase materials or supplies from entities that are associated with a party that meets the criteria of a related party of the Company. These transactions are reviewed quarterly and to date have not been material to the Company's consolidated financial statements.

15. 401(k) Plan

In 2015, the Company established the Intellia Therapeutics, Inc. 401(k) Plan (the "401(k) Plan") for its employees, which is designed to be qualified under Section 401(k) of the Internal Revenue Code. Eligible employees are permitted to contribute to the 401(k) Plan within statutory and 401(k) Plan limits. The Company makes matching contributions of 50% of the first 6% of employee contributions. The Company made matching contributions of $0.8 million and $0.6 million for the years ended December 31, 2019 and 2018, respectively.

16. Unaudited Quarterly Results

The results of operations on a quarterly basis for the years ended December 31, 2019 and 2018 are set forth below:

	March 31, 2019	June 30, 2019	September 30, 2019	December 31, 2019
	(Amounts in thousands except per share data)			
Collaboration revenue	$ 10,433	$ 11,118	$ 10,616	$ 10,936
Operating expenses:				
Research and development	23,709	25,460	27,513	31,731
General and administrative	10,533	13,118	8,431	8,976
Total operating expenses	34,242	38,578	35,944	40,707
Operating loss	(23,809)	(27,460)	(25,328)	(29,771)
Interest income	1,869	1,777	1,694	1,495
Net loss	$ (21,940)	$ (25,683)	$ (23,634)	$ (28,276)
Net loss per share, basic and diluted	$ (0.49)	$ (0.56)	$ (0.49)	$ (0.57)
Weighted average shares outstanding, basic and diluted	45,234	45,814	48,554	49,350

	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(Amounts in thousands except per share data)			
Collaboration revenue	$ 7,469	$ 7,677	$ 7,408	$ 7,880
Operating expenses:				
Research and development	22,493	23,467	23,237	19,918
General and administrative	7,406	7,805	8,270	8,708
Total operating expenses	29,899	31,272	31,507	28,626
Operating loss	(22,430)	(23,595)	(24,099)	(20,746)
Interest income	1,074	1,376	1,397	1,680
Net loss	$ (21,356)	$ (22,219)	$ (22,702)	$ (19,066)
Net loss per share, basic and diluted	$ (0.51)	$ (0.52)	$ (0.53)	$ (0.43)
Weighted average shares outstanding, basic and diluted	42,043	42,836	43,161	44,215

EXHIBIT INDEX

Exhibit No.	Exhibit Index
3.1	Second Amended and Restated Certificate of Incorporation of the Registrant (1)
3.2	Second Amended and Restated By-laws of the Registrant (1)
4.1	Investors' Rights Agreement among the Registrant and certain of its stockholders, dated August 20, 2015 (5)
4.2	Amendment No. 1 to Investors' Rights Agreement among the Registrant and certain of its stockholders, dated April 11, 2016 (6)
4.3	Amendment No. 2 to Investors' Rights Agreement among the Registrant and certain of its stockholders, dated August 25, 2016 (3)
4.4*	Description of Certain Registrant's Securities
10.1#	2015 Amended and Restated Stock Option and Incentive Plan and forms of award agreements thereunder (3)
10.2#	Senior Executive Cash Incentive Bonus Plan (5)
10.3†	License Agreement dated as of July 16, 2014 by and between the Registrant (as successor in interest of Intellia Therapeutics, LLC) and Caribou Biosciences, Inc. (4)
10.4†	Services Agreement dated as of July 16, 2014 by and between the Registrant (as successor in interest of Intellia Therapeutics, LLC) and Caribou Biosciences, Inc. (4)
10.5†	License and Collaborative Research Agreement dated as of December 18, 2014 by and between the Registrant and Novartis Institutes for BioMedical Research, Inc. (2)
10.6#	Form of Indemnification Agreement (3)
10.7	Lease Agreement, by and between the Registrant and MIT 130 Brookline LLC, dated as of October 21, 2014 (5)
10.8	Lease Agreement, by and between the Registrant and BMR-Sidney Research Campus LLC, dated as of January 6, 2016 (5)
10.9#	2016 Employee Stock Purchase Plan (3)
10.10†	Amendment No. 1 to License Agreement dated as of February 2, 2016 by and between the Registrant and Caribou Biosciences, Inc. (5)
10.11†	Addendum to License Agreement dated as of February 2, 2016 by and between the Registrant and Caribou Biosciences, Inc. (5)
10.12†	License and Collaboration Agreement dated as of April 11, 2016 by and between the Registrant and Regeneron Pharmaceuticals, Inc. (2)
10.13	Common Stock Purchase Agreement dated as of April 26, 2016 between the Registrant and Regeneron Pharmaceuticals, Inc. (3)
10.14	Common Stock Purchase Agreement dated as of April 26, 2016 between the Registrant and Novartis Institutes for BioMedical Research, Inc. (3)
10.15#	Form of Employment Agreement for Executive Officers (3)
10.16†	Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement dated December 15, 2016 by and between the Registrant, CRISPR Therapeutics AG, The Regents of the University of California, University of Vienna, ERS Genomics Ltd., TRACR Hematology Ltd., Caribou Biosciences, Inc., and Dr. Emmanuelle Charpentier (7)

Exhibit No.	Exhibit Index
10.17#	Form of Amended and Restated Employment Agreement (8)
10.18†	Letter Agreement, dated as of July 20, 2018, by and between the Company and Regeneron Pharmaceuticals, Inc. and the corresponding Form of Co-Development and Co-Promotion Agreement, by and between the Company and Regeneron Pharmaceuticals, Inc. (9)
10.19†	Agreement and Amendment to License and Collaborative Research Agreement, dated as of December 3, 2018, by and between Novartis and the Company (10)
10.20	First Amendment to Lease, dated as of April 5, 2019, by and between the Company and MIT 130 Brookline Leasehold LLC. (11)
10.21#*	Second Amended and Restated Non-Employee Director Compensation Policy
21.1*	Subsidiaries of the Registrant
23.1*	Consent of Deloitte & Touche LLP, Independent Registered Public Accounting Firm
31.1*	Certification of Chief Executive Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2*	Certification of Chief Financial Officer pursuant to Rules 13a-14(a) or 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1	Certifications pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of The Sarbanes-Oxley Act of 2002, by John M. Leonard, M.D., President and Chief Executive Officer of the Company, and Glenn Goddard, Executive Vice President, Chief Financial Officer of the Company (12)
101.INS*	Inline XBRL Instance Document.
101.SCH*	Inline XBRL Taxonomy Extension Schema Document.
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104*	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101*)

† Application for confidential treatment of certain provisions has been granted by the Securities and Exchange Commission. Omitted material for which confidential treatment has been requested has been filed separately with the Securities and Exchange Commission.

* Filed herewith.

\# Indicates a management contract or any compensatory plan, contract or arrangement

(1) Incorporated by reference to the Registrant's Current Report on Form 8-K (File No. 001-37766) filed with the Securities and Exchange Commission on May 17, 2016

(2) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-210689) filed with the Securities and Exchange Commission on May 5, 2016

(3) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-210689) filed with the Securities and Exchange Commission on April 27, 2016

(4) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-210689) filed with the Securities and Exchange Commission on April 19, 2016

(5) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-210689) filed with the Securities and Exchange Commission on April 11, 2016

(6) Incorporated by reference to the Registration Statement on Form S-1 (File No. 333-210689) filed with the Securities and Exchange Commission on April 12, 2016

(7) Incorporated by reference to the Registrant's Current Report on Form 8-K (File No. 001-37766) filed with the Securities and Exchange Commission on December 16, 2016
(8) Incorporated by reference to the Registrant's Current Report on Form 8-K (File No. 001-37766) filed with the Securities and Exchange Commission on April 17, 2018
(9) Incorporated by reference to the Registrant's Quarterly Report on Form 10-Q (File No. 001-37766) filed with the Securities and Exchange Commission on October 31, 2018
(10) Incorporated by reference to the Registrant's Annual Report on Form 10-K (File No. 001-37766) filed with the Securities and Exchange Commission on February 27, 2019
(11) Incorporated by reference to the Registrant's Quarterly Report on Form 10-Q (File No. 001-37766) filed with the Securities and Exchange Commission on May 2, 2019
(12) The certifications furnished in Exhibit 32.1 hereto are deemed to accompany this Annual Report on Form 10-K and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

INTELLIA THERAPEUTICS, INC.

By: /s/ John M. Leonard
John M. Leonard, M.D.
President and Chief Executive Officer

Dated: February 27, 2020

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ John M. Leonard John M. Leonard, M.D.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	February 27, 2020
/s/ Glenn Goddard Glenn Goddard	Executive Vice President, Chief Financial Officer *(Principal Financial and Accounting Officer)*	February 27, 2020
/s/ Fred Cohen Fred Cohen	Director	February 27, 2020
/s/ Caroline Dorsa Caroline Dorsa	Director	February 27, 2020
/s/ Jean François Formela Jean François Formela, M.D.	Director	February 27, 2020
/s/ Jesse Goodman Jesse Goodman	Director	February 27, 2020
/s/ Perry Karsen Perry Karsen	Director	February 27, 2020
/s/ Frank Verwiel Frank Verwiel, M.D.	Director	February 27, 2020