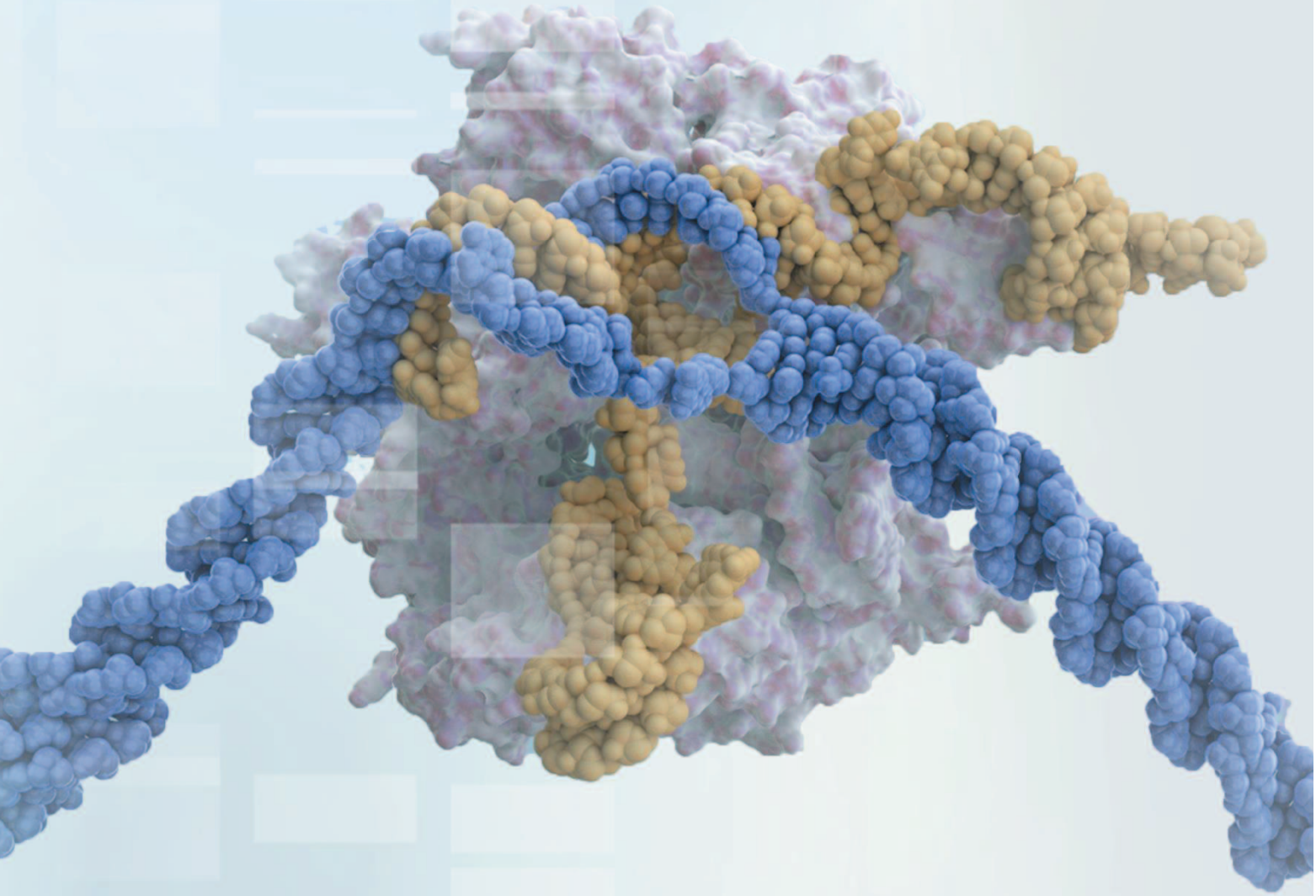
CRISPR THERAPEUTICS

ANNUAL REPORT
2018

Transformative Gene-Based Medicines
For Serious Human Diseases



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, 2018

OR

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

FOR THE TRANSITION PERIOD FROM TO

Commission File Number 001-37923

CRISPR THERAPEUTICS AG

(Exact name of Registrant as specified in its Charter)

Switzerland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Baarerstrasse 14 **6300 Zug, Switzerland**	
(Address of principal executive offices)	**Not Applicable** **(Zip Code)**

Registrant's telephone number, including area code: +41 (0)41 561 32 77

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

Common shares, nominal value CHF 0.03 per share	The Nasdaq Global Market
Title of each class	**Name of each exchange on which registered**

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

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

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

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

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

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

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a small reporting company)	Small 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 ☒

As of June 30, 2018, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $2.7 billion, based on the closing price of the registrant's common stock on June 29, 2018 (the last trading day of the registrant's second fiscal quarter of 2018).

As of February 21 2019, 52,279,167 common shares were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement relating to the Annual General Meeting of Shareholders for the year ended December 31, 2018, which the registrant intends to file with the Securities and Exchange Commission pursuant to Regulation 14A within 120 days after the end of the registrant's fiscal year ended December 31, 2018, are incorporated by reference into Part III of this Report.

Table of Contents

Throughout this Annual Report on Form 10-K, the "Company," "CRISPR," "CRISPR Therapeutics," "we," "us," and "our," except where the context requires otherwise, refer to CRISPR Therapeutics AG and its consolidated subsidiaries, and "our board of directors" refers to the board of directors of CRISPR Therapeutics AG.

Special Note Regarding Forward-Looking Statements and Industry Data

This Annual Report on Form 10-K contains forward-looking statements regarding, among other things, our future discovery and development efforts, our future operating results and financial position, our business strategy, and other objectives for our operations. The words "anticipate," "believe," "intend," "expect," "may," "estimate," "predict," "project," "potential" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. There are a number of important risks and uncertainties that could cause our actual results to differ materially from those indicated by forward-looking statements. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the section entitled "Risk Factors" in Part I that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this Annual Report on Form 10-K are made as of the date of this Annual Report on Form 10-K, and we do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

This Annual Report on Form 10-K includes statistical and other industry and market data, which we obtained from our own internal estimates and research, as well as from industry and general publications and research, surveys, and studies conducted by third parties. Industry publications, studies, and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe that each of these studies and publications is reliable, we have not independently verified market and industry data from third-party sources. While we believe our internal company research is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source.

Investors and others should note that we announce material financial information to our investors using our investor relations website (https://crisprtx.gcs-web.com/), SEC filings, press releases, public conference calls and webcasts. We use these channels as well as social media to communicate with the public about our company, our business, our product candidates and other matters. It is possible that the information we post on social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the social media channels listed on our investor relations website.

PART I

Item 1. Business.

BUSINESS

Overview

We are a leading gene editing company focused on the development of CRISPR/Cas9-based therapeutics. CRISPR/Cas9 stands for Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) and is a revolutionary technology for gene editing, the process of precisely altering specific sequences of genomic DNA. We aim to apply this technology to disrupt, delete, correct and insert genes to treat genetically-defined diseases and to engineer advanced cellular therapies. We believe that our scientific expertise, together with our gene editing approach, may enable an entirely new class of highly effective and potentially curative therapies for patients with both rare and common diseases for whom current biopharmaceutical approaches have had limited success. Our most advanced programs target the genetically-defined diseases transfusion-dependent beta thalassemia (TDT) and severe sickle cell disease (SCD), two hemoglobinopathies with high unmet medical need. We are also progressing several gene-edited allogeneic cell therapy programs, beginning with three allogeneic chimeric antigen receptor T cell, or CAR-T candidates for the treatment of hematological and solid tumor cancers.

The use of CRISPR/Cas9 for gene editing was derived from a naturally occurring viral defense mechanism in bacteria and has been described by leading scientific journals as a breakthrough technology. The application of CRISPR/Cas9 for gene editing was co-invented by one of our scientific founders, Dr. Emmanuelle Charpentier, the Acting and Founding Director of the Max Planck Unit for the Science of Pathogens and a Director at the Max Planck Institute for Infection Biology, both in Berlin, Germany. Dr. Charpentier and her collaborators published work elucidating the mechanism by which the Cas9 endonuclease, a key component of CRISPR/Cas9, can be programmed to cut double-stranded DNA at specific locations. We have acquired rights to the intellectual property encompassing CRISPR/Cas9 and related technologies from Dr. Charpentier and continue to strengthen our intellectual property estate through our own research and additional in-licensing efforts, furthering our leadership in the development of CRISPR/Cas9-based therapeutics.

Our product development and partnership strategies are designed to exploit the full potential of the CRISPR/Cas9 platform while maximizing the probability of successfully developing our product candidates. For our most advanced product candidates, we have taken an *ex vivo* approach in which we edit cells outside of the human body using CRISPR/Cas9 before administering them to the patient. We are also pursuing select *in vivo* applications, in which we deliver the CRISPR/Cas9-based therapeutic directly to target cells within the human body.

Our lead product candidate, CTX001™, is an investigational *ex vivo* CRISPR gene-edited therapy that is being evaluated for patients suffering from TDT or severe SCD in which a patient's hematopoietic stem cells are engineered to produce high levels of fetal hemoglobin (HbF; hemoglobin F) in red blood cells. HbF is a form of the oxygen carrying hemoglobin that is naturally present at birth and is then replaced by the adult form of hemoglobin. The elevation of HbF by CTX001 has the potential to alleviate transfusion requirements for TDT patients and painful and debilitating sickle crises for SCD patients. CTX001 is being developed under a co-development and co-commercialization agreement between CRISPR Therapeutics and Vertex Pharmaceuticals, Inc ("Vertex").

Beta Thalassemia

We and Vertex are investigating CTX001 in a Phase 1/2 open-label clinical trial designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with TDT, non-beta zero/beta zero subtypes. The first two patients in the trial will be treated sequentially and, pending data from these initial two patients, the trial will open for broader concurrent enrollment. The first patient has been treated with CTX001 in this trial. The study is currently being conducted at multiple clinical trial sites in Canada and Europe. In addition, CRISPR Therapeutics and Vertex expanded the U.S. Investigational New Drug Application (IND) for CTX001 to include beta thalassemia.

Sickle Cell Disease

We and Vertex are also investigating CTX001 in a Phase 1/2 open-label clinical trial designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with severe SCD. Similar to the trial in beta thalassemia, the first two patients in the trial will be treated sequentially and, pending data from these initial two patients, the trial will open for broader concurrent enrollment. The first patient has been enrolled in this trial. The study is currently being conducted at clinical trial sites in the U.S. CTX001 was granted Fast Track Designation by the U.S. Food and Drug Administration (the "FDA") for the treatment of SCD. In addition, CRISPR Therapeutics and Vertex have obtained approvals of Clinical Trial Applications (CTAs) for CTX001 for SCD in Canada and additional countries in Europe.

Immuno-Oncology

We believe CRISPR/Cas9 has the potential to create the next generation of CAR-T cell therapies that may have a superior product profile compared to current autologous therapies and allow accessibility to broader patient populations. Drawing from the *ex vivo* gene editing capabilities gained through our lead programs, we are advancing several immuno-oncology cell therapy programs including our lead candidate, CTX110™, a healthy donor-derived gene-edited allogeneic CAR-T therapy targeting cluster of differentiation 19, or CD19, positive malignancies. In preclinical studies, we observed that CTX110 prolonged the survival of mice with a CD19-positive xenograft tumor model. In addition, we have two additional allogeneic CAR-T programs, CTX120™ targeting B-cell maturation antigen (BCMA) in development for the treatment of multiple myeloma; and CTX130™, targeted towards CD70, in development for the treatment of both solid tumors and hematologic malignancies. In preclinical studies of CTX120, we observed complete tumor elimination in a xenograft multiple myeloma tumor model in all mice treated with CTX120 across multiple dose cohorts. Similarly, in preclinical studies of CTX130, we observed complete tumor elimination in a xenograft model of renal cell carcinoma in all mice treated with CTX130.

Other Programs

To further expand the applications of our *ex vivo* gene-editing expertise, we have increased our efforts in the field of regenerative medicine. Regenerative medicine, or the use of stem cells to repair or replace tissue or organ function lost due to disease, damage or age, holds the potential to treat both rare and common diseases. We are pursuing gene-editing approaches to allow allogeneic use of stem cell-derived therapies by enabling immune evasion, improving existing cell function and directing cell fate using CRISPR/Cas9. Our first major effort in this area is in diabetes together with our partner, ViaCyte Incorporated ("ViaCyte").

In addition to our *ex vivo* programs, we are pursuing a number of in *vivo* gene editing programs. Our initial *in vivo* applications target diseases of the liver, lung and muscle and leverage well-established delivery technologies for gene-based therapeutics, such as lipid nanoparticle-based delivery vehicles, or LNPs, and adeno-associated viral vectors, or AAV vectors.

Given the numerous potential therapeutic applications for CRISPR/Cas9, we have partnered strategically to broaden the indications we can pursue and accelerate development of programs by accessing specific technologies and/or disease-area expertise. In 2015, we established a joint venture, called Casebia Therapeutics LLP ("Casebia"), with Bayer HealthCare ("Bayer") and its subsidiaries in which we have a 50% interest, and a collaboration agreement with Vertex to pursue specific indications where these companies have outstanding and distinctive capabilities. In December 2017, we entered into a joint development and commercialization agreement with Vertex to co-develop and co-commercialize CTX001 as part of our existing collaboration. The significant resource commitments by Bayer and Vertex underscore the potential of our platform, as well as their dedication to developing transformative CRISPR/Cas9-based therapeutics. In September 2018, we entered into a Research and Collaboration Agreement with ViaCyte on the discovery, development and commercialization of gene-edited allogeneic stem cell therapies for the treatment of diabetes. The combination of ViaCyte's stem cell capabilities and our gene editing capabilities has the potential to enable a beta-cell replacement product that may deliver durable benefit to patients without the need for immune suppression.

Our mission is to create transformative gene-based medicines for serious human diseases. We believe that our highly experienced team, together with our scientific expertise, product development strategy, partnerships and intellectual property, position us as a leader in the development of CRISPR/Cas9-based therapeutics.

Gene Editing Background

There are thousands of diseases caused by aberrant DNA sequences. Traditional small molecule and biologic therapies have had limited success in treating many of these diseases because they fail to address the underlying genetic causes. Newer approaches such as RNA therapeutics and viral gene therapy more directly target the genes related to disease, but each has clear limitations. RNA-based therapies, such as mRNA and siRNA, face challenges with repeat dosing and related toxicities. Non-integrating viral gene therapy platforms, such as AAV, may have limited durability because they do not permanently change the genome and have limited efficacy upon re-administration due to resulting immune responses. Integrating viral gene therapy platforms, such as lentivirus, permanently alter the genome but do so randomly, which leads to the potential for undesirable mutations. Additionally, cells may recognize the transduced genes as foreign and respond by reducing their expression, limiting their efficacy. Thus, while our understanding of genetic diseases has increased tremendously since the mapping of the human genome, our ability to treat them effectively has been limited.

We believe gene editing has the potential to enable a next generation of therapeutics and provide potentially curative therapies to many genetic diseases through precise gene modification. The process of gene editing involves precisely altering DNA sequences within the genomes of cells using enzymes to cut the DNA at specific locations. After a cut is made, natural cellular processes repair the DNA to either silence or correct undesirable sequences, potentially reversing their negative effects. Importantly, because the genome itself is modified in this process, the change is permanent in the patient.

Furthermore, the ability to alter DNA sequences precisely has applications beyond the treatment of genetically-defined diseases. CRISPR/Cas9 gene editing could also enable the engineering of genomes of cell-based therapies to make them more efficacious, safer and available to a broader group of patients. Cell therapies have already begun to make a meaningful impact in certain diseases and gene editing could help accelerate that progress across diverse disease areas, including oncology and diabetes.

Earlier generations of gene-editing technologies, such as zinc finger nucleases (ZFNs), transcription-activator like effector nucleases (TALENs) and meganucleases, rely on engineered protein-DNA interactions. While these systems were an important first step to demonstrate the potential of gene editing, their development has been challenging in practice due to the complexity of engineering protein-DNA interactions. In contrast, CRISPR/Cas9 is guided by RNA-DNA interactions, which are more predictable and straightforward to engineer and apply.

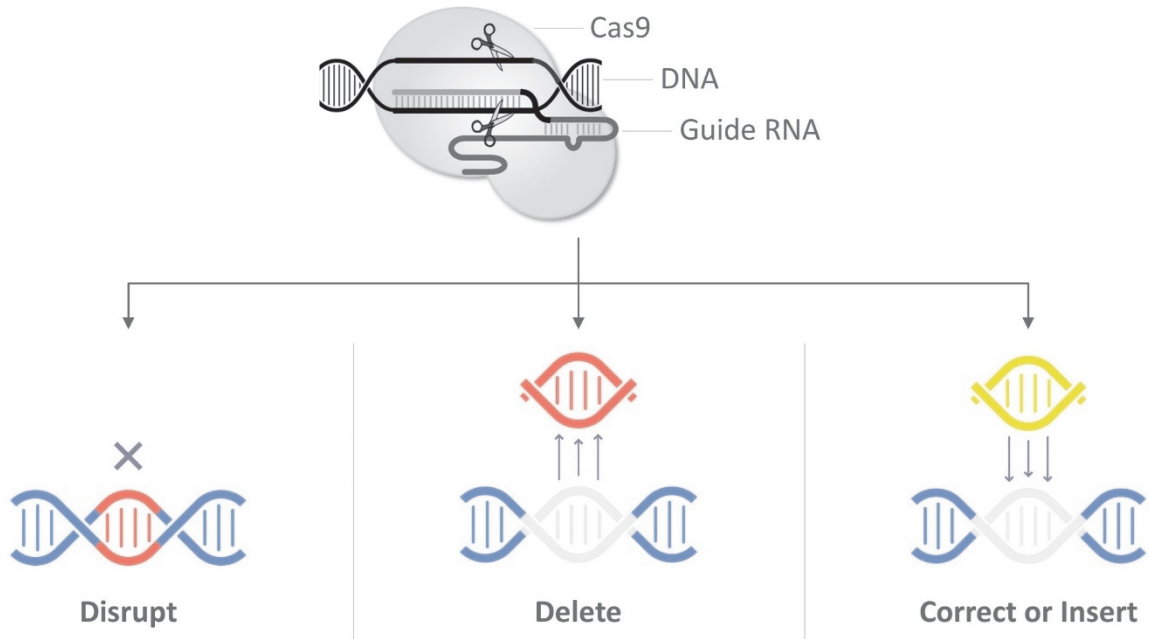
The CRISPR/Cas9 Technology

CRISPR/Cas9 evolved as a naturally occurring defense mechanism that protects bacteria against viral infections. Dr. Emmanuelle Charpentier and her collaborators elucidated this mechanism and developed ways to adapt and simplify it for use in gene editing. The CRISPR/Cas9 technology they described consists of three basic components: CRISPR-associated protein 9, or Cas9, CRISPR RNA, or crRNA, and trans-activating CRISPR RNA, or tracrRNA. Cas9, in combination with these two RNA molecules, is described as "molecular scissors" that can make specific cuts and edits in selected double-stranded DNA.

Dr. Emmanuelle Charpentier and her collaborators further simplified the system for use in gene editing by combining the crRNA and tracrRNA into a single RNA molecule called a guide RNA. The guide RNA binds to Cas9 and can be programmed to direct the Cas9 enzyme to a specific DNA sequence based on Watson-Crick base pairing rules. The CRISPR/Cas9 technology can be used to make cuts in DNA at specific sites of targeted genes, providing a powerful tool for developing gene editing-based therapeutics.

Once the DNA is cut, the cell uses naturally occurring DNA repair mechanisms to rejoin the cut ends. If a single cut is made, a process called non-homologous end joining can result in the addition or deletion of base pairs, disrupting the original DNA sequence and causing gene inactivation. A larger fragment of DNA can also be deleted by using two guide RNAs that target separate sites. After cleavage at each site, non-homologous end joining unites the separate ends, deleting the intervening sequence. Alternatively, if a DNA template is added alongside the CRISPR/Cas9 machinery, the cell can correct a gene or even insert a new gene through a process called homology directed repair.

CRISPR/Cas9 gene editing

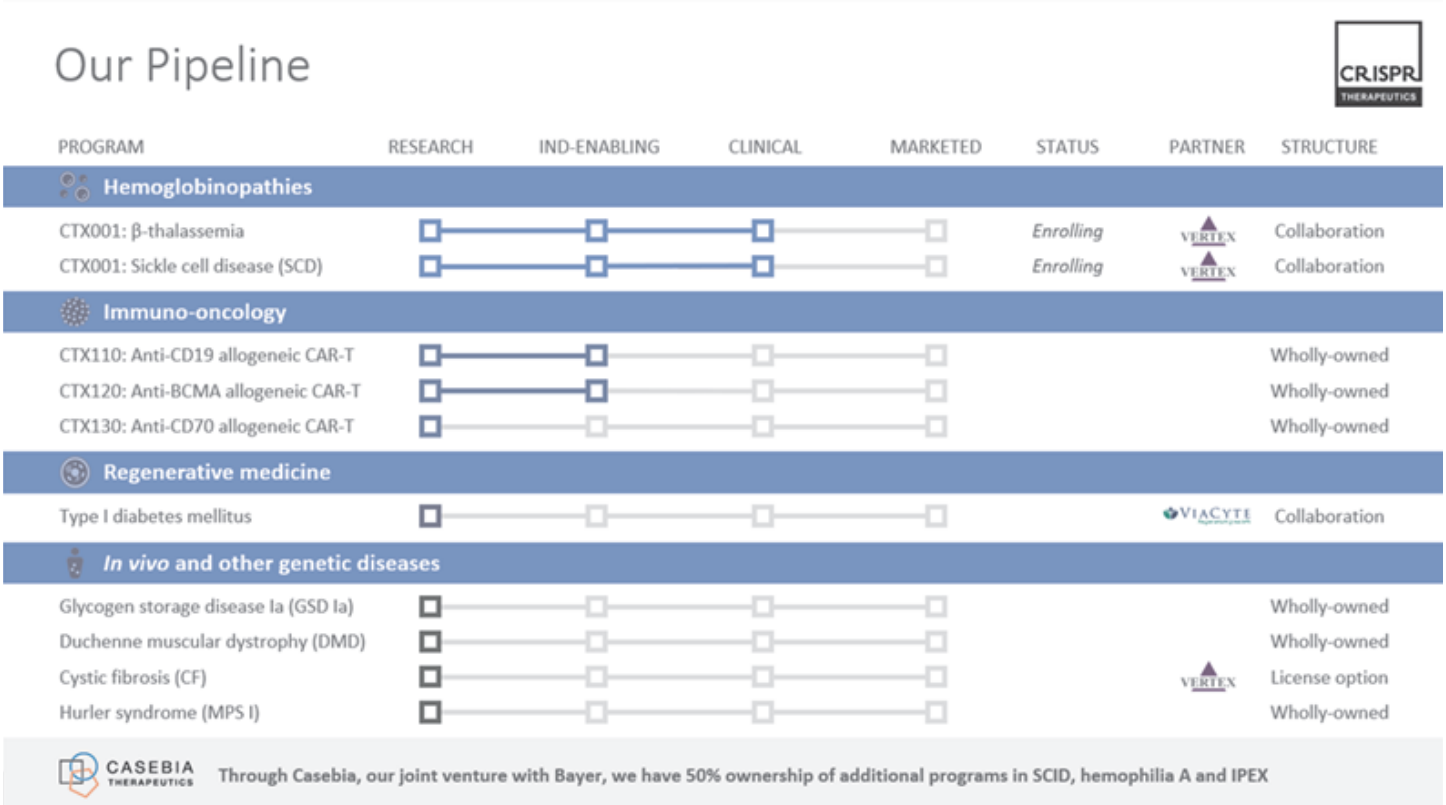


We believe that CRISPR/Cas9 is a versatile technology that can be used to disrupt, delete, correct or insert genes. We intend to take advantage of the versatility and modularity of the CRISPR/Cas9 system to adapt and rapidly customize individual components for

specific disease applications. Consequently, we believe that CRISPR/Cas9 may form the basis of a new class of therapeutics with the potential to treat both rare and common diseases.

Our Pipeline

The following table summarizes the status of our product development pipeline:



Hematopoietic Programs

Background

We are primarily utilizing *ex vivo* approaches to treat diseases related to the hematopoietic system, which is the system of organs and tissues, such as bone marrow, the spleen and lymph nodes, involved in the production of blood. Today, many of the hematopoietic system diseases we are targeting are treated with allogeneic hematopoietic stem cell transplants, or allo-HSCT. In performing allo-HSCT, physicians replace a patient's blood-forming cells that contain the defective gene with cells obtained from a different person that contain the normal gene. Unfortunately, not all patients are able to be matched with suitable donors. Patients who do undergo allo-HSCT face a high risk of complications such as infections related to immunosuppression, transplant rejection and graft-versus-host disease, where immune cells in the transplanted tissue (the graft) recognize the recipient (the host) as "foreign" and begin to attack the host's cells.

In contrast to allo-HSCT, our approach is to harvest stem cells directly from the patient, edit the target gene *ex vivo*, and reintroduce those same cells back into the patient. We believe this *ex vivo* gene editing approach, which uses the patient's own cells, may provide better results than allo-HSCT.

Our Lead Programs—Hemoglobinopathies

Hemoglobinopathies are a diverse group of inherited blood disorders that result from variations in the synthesis or structure of hemoglobin. Our lead programs in hemoglobinopathies, for which we have partnered with Vertex, aim to develop a single, potentially curative CRISPR/Cas9-based therapy to treat both beta thalassemia and SCD. These diseases are caused by mutations in the gene encoding the beta globin protein. Beta globin is an essential component of hemoglobin, a protein in red blood cells that delivers oxygen and removes carbon dioxide throughout the body. Several factors make these attractive lead indications, including: (i) high

unmet medical need, (ii) compelling market potential, (iii) well-understood genetics and (iv) the ability to employ an *ex vivo* gene disruption strategy.

Beta Thalassemia

Overview

Beta thalassemia is a blood disorder that is associated with a reduction in the production of hemoglobin. This disease is caused by mutations that give rise to the insufficient expression of the beta globin protein, which can lead to symptoms related not only to the lack of hemoglobin, but also to the buildup of unpaired alpha globin proteins in red blood cells. The severity of symptoms associated with beta thalassemia varies depending on the levels of functional beta globin present in the blood cells. The unpaired alpha globin chains are toxic to red blood cells and reduce red blood cell lifespan. In the most severe cases, described as beta thalassemia major, functional beta globin is either completely absent or reduced, resulting in severe anemia. In these patients, the bone marrow cannot keep pace with the destruction of red blood cells, and thus these patients require periodic blood transfusions. While chronic blood transfusions can be effective at addressing symptoms, they often lead to iron overload, progressive heart and liver failure, and eventually death. Patients with mild forms of beta thalassemia may experience some mild anemia or even be asymptomatic. The total worldwide incidence of beta thalassemia is estimated to be 60,000 births annually, the total prevalence in the United States and the European Union is estimated to be approximately 19,000 and there are over 200,000 people worldwide who are alive and registered as receiving treatment for the disease.

Limitations of current treatment options

The most common treatment for beta thalassemia is chronic blood transfusions. Patients typically receive transfusions every two to four weeks and chronic administration of blood often leads to elevated levels of iron in the body and can cause organ damage over a relatively short period of time. Patients are often given iron chelators, or medicines to reduce iron levels in the blood, which are associated with their own significant toxicities. Low adherence to this burdensome regime often results in death by 30 years of age for patients with transfusion-dependent beta thalassemia. The only potentially curative therapy for this disease is allo-HSCT, but few patients elect to have this procedure given its associated morbidity and mortality. In developing countries, where chronic transfusions are not available, most patients die in early childhood. We believe that our therapeutic approach could offer a potentially curative therapy for this devastating disease.

Sickle Cell Disease

Overview

SCD is an inherited disorder of red blood cells resulting from a specific mutation in the beta globin gene that causes abnormal red blood cell function. Under conditions of low oxygen concentration, the abnormal hemoglobin proteins aggregate within the red blood cells causing them to become sickled in shape and inflexible. These sickled cells obstruct blood vessels, restricting blood flow to organs, ultimately resulting in anemia, severe pain, infections, stroke, overall poor quality of life and early death. The worldwide incidence of SCD is estimated to be 300,000 births annually and there are 20-25 million people worldwide with the disease. In the United States, the total prevalence is estimated to be 100,000 individuals.

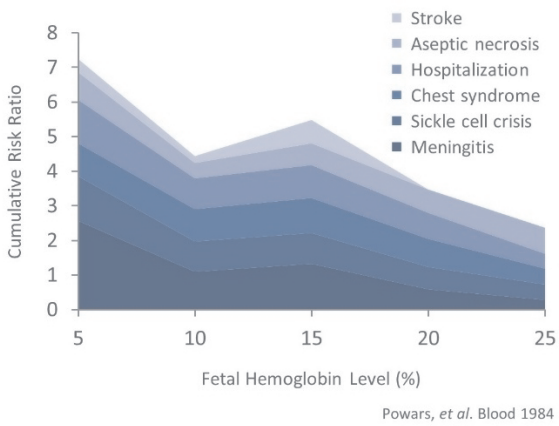
Limitations of current treatment options

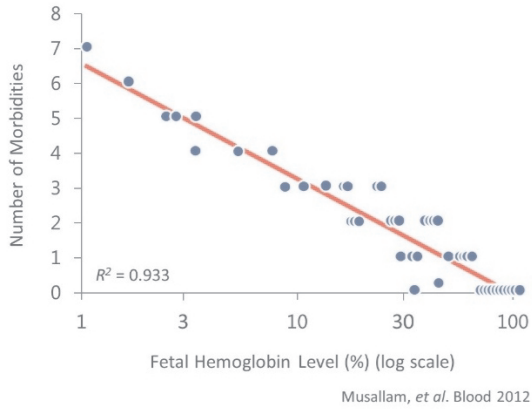
As with beta thalassemia, in regions where access to modern medical care is available, standard treatment for SCD involves chronic blood transfusions, which has the same associated risks of iron overload and toxicities associated with chelation therapy. Allo-HSCT is a second potential treatment option. While allo-HSCT provides the only potentially curative therapeutic path for SCD, it is often avoided given the significant risk of transplant-related morbidity and mortality in these patients.

Our Gene Editing Approach

Our therapeutic approach to treating beta thalassemia and SCD employs gene editing to upregulate the expression of the gamma globin protein, a hemoglobin subunit that is commonly present only in newborn infants. Hemoglobin that contains gamma globin instead of beta globin protein is referred to as fetal hemoglobin, or HbF. In most individuals HbF disappears in infancy as gamma globin is replaced by beta globin through naturally occurring suppression of the gamma globin gene. The symptoms of beta thalassemia and SCD typically do not manifest until several months after birth, when the levels of HbF have declined considerably. Some patients with beta thalassemia or SCD have elevated levels of HbF that persist into adulthood, a condition known as hereditary persistence of fetal hemoglobin, or HPFH. Patients with HPFH are often asymptomatic, or experience much milder forms of disease. This protective HPFH condition has been shown to result from specific changes to these patients' genomic DNA, either in the region of the globin genes or in certain genetic regulatory elements that control the expression levels of the globin genes.

Relationship between level of HbF and morbidity in sickle cell disease and beta thalassemia





An alternative CRISPR/Cas9 approach to treating hemoglobinopathies would be to correct the mutated beta globin gene. We have chosen the HbF upregulation strategy as our initial approach given the relative technical simplicity of the gene disruption strategy involved, the ability of this strategy to counteract a wide variety of different beta globin mutations, and the absence of symptoms in patients with high HbF levels.

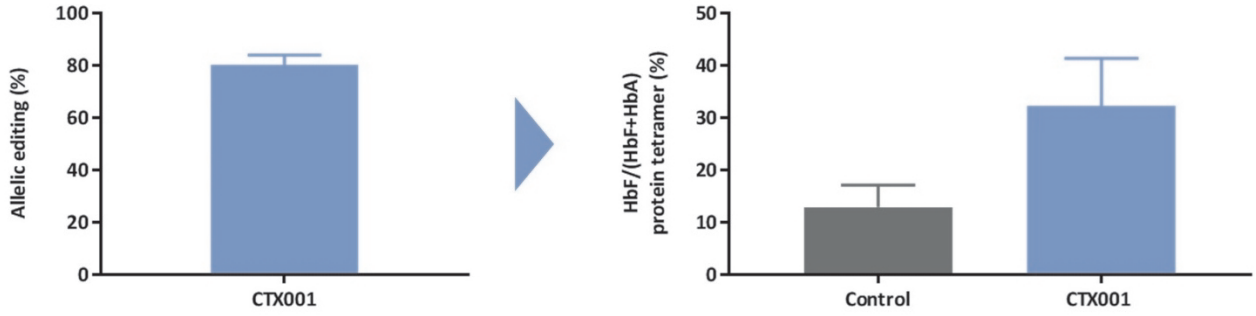
Our Lead Hemoglobinopathies Product Candidate—CTX001

Our lead product candidate, CTX001, uses CRISPR/Cas9 to mimic the high levels of HbF that occur naturally in HPFH patients. To achieve this effect, CTX001 uses CRISPR/Cas9 to disrupt the erythroid specific enhancer of the BCL11A gene. This gene encodes the BCL11A protein, a critical factor that keeps HbF levels low in most individuals. Disrupting the BCL11A erythroid specific enhancer reduces BCL11A expression specifically in erythroid lineage cells, thereby upregulating expression of gamma globin and increasing HbF levels.

Our therapeutic approach involves isolating hematopoietic stem cells, or HSCs, which give rise to red blood cells, from a patient, treating those cells *ex vivo* with CRISPR/Cas9 to disrupt the BCL11A erythroid specific enhancer and reintroducing the edited cells back into the patient. We believe that once reintroduced into the patient, these genetically modified stem cells will produce red blood cells that contain high levels of HbF. In beta thalassemia, elevating HbF may reduce the toxicity of unpaired alpha globin chains, thereby increasing red blood cell lifespan. Consequently, CTX001 may have the potential to reduce or even eliminate the need for transfusions in these patients. In SCD, elevated HbF may prevent a cell from sickling, and so achieving sufficiently high HbF in most red blood cells could significantly reduce or eliminate the symptoms associated with the disease.

In preclinical studies using CTX001, our CRISPR/Cas9 gene editing process demonstrated the ability to edit HSCs with approximately 80% allelic editing efficiency at clinical scale in a bulk population of cells. We observed this high editing efficiency across all stem cell subsets, including in long-term repopulating HSCs. After erythroid differentiation, this editing resulted in HbF accounting for greater than 30% of total hemoglobin in edited cells, compared to approximately 10% HbF in the control arm of the study.

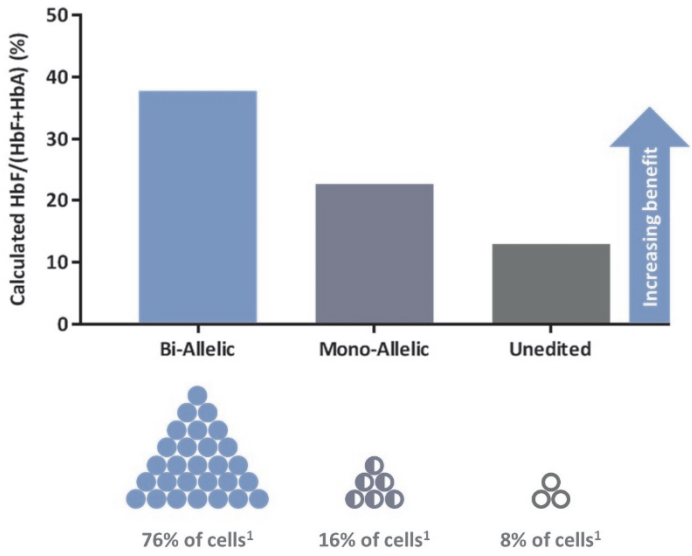
Editing efficiency in human CD34+ cells and resulting HbF ratio after erythroid differentiation



Performed at clinical scale with n=6 healthy donors

On a per cell basis, more than 90% of cells had modifications at the desired location, with 76% of the cells having edits in both copies of the target gene and 16% of the cells having edits made on one copy of the target gene. We estimate that this editing rate results in HbF expression levels of greater than 35% in cells that have edits on both copies of the target gene, and over 20% for cells edited at one gene.

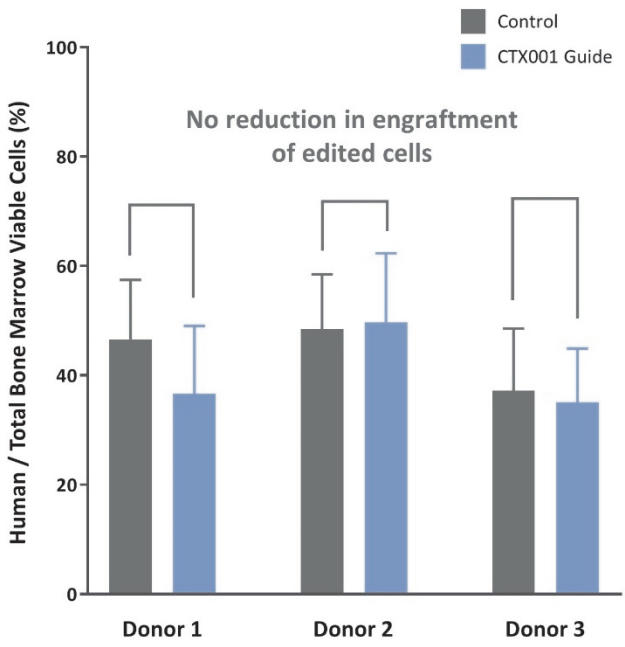
Estimated HbF expression at the cellular level



1. n=163 single erythroid colonies derived from edited CD34+ cells from healthy donors

In preclinical mouse models designed to test the safety of CTX001, gene-edited HSCs maintained the ability to engraft long term and to differentiate into multiple lineages. Toxicology studies revealed no significant findings and no difference in the biodistribution of edited cells compared to controls. Finally, no off-target activity was detectable for the CTX001 guide RNA after assessing over 5,000 homology-based sites and over 2,000 homology-independent sites.

CTX001 engraftment *in vivo* in mice[1]



1. 16-week engraftment data

We believe our CRISPR/Cas9 gene editing strategy may have significant advantages over other gene therapies in development for the treatment of hemoglobinopathies. For example, lentivirus-based treatments involve a random integration of one or more copies of the globin gene throughout the genome. The expression levels of the newly introduced gene can vary depending on the exact location of the DNA in the genome, leading to inconsistent and variable levels of expression. We believe our strategy may lead to more uniform globin expression across a high percentage of cells. In addition, with each random lentiviral integration, a mutation may be created, which may have an associated safety concern, including the potential to cause cancer. In contrast, CRISPR/Cas9 targets a specific genomic site for editing, and we have detected no off-target activity for our CTX001 guide RNA.

Immuno-Oncology Programs

Over the past several years, interest in the oncology community has grown rapidly in the field of immuno-oncology, or treatments that harness the immune system to attack cancer cells. Engineered immune cell therapy is one such approach, in which immune system cells such as T cells are genetically modified to enable them to recognize and attack cancerous cells.

Engineered cell therapy has demonstrated encouraging results leading to two approvals for autologous CD19-targeted CAR-T products, and may become an entirely new class of oncology therapeutics; however, realizing this full potential will require overcoming some key challenges. Most engineered cell therapies in development require unique products to be created for each patient treated, an approach that has in the past proven challenging and cost prohibitive in the field of oncology. Additionally, these versions of engineered cell therapies appear limited in their ability to treat solid tumors and have demonstrated sub-optimal safety profiles. In contrast, allogeneic engineered T cell therapies could have immediate availability because of their ability to be administered “off-the-shelf”, improved potency due to the use of healthy-donor starting material, greater consistency since each batch yields many doses, improved access by avoiding the need for patient apheresis, and flexible dosing, whether through dose titration or re-dosing.

We expect that the cellular engineering strategies that are ultimately successful in immuno-oncology will involve multiple genetic modifications, an application for which we believe CRISPR/Cas9 will play a central role. While other gene editing platforms could potentially be used for these purposes, CRISPR/Cas9 is particularly well-suited for multiplexed editing, which is the modification and/or insertion of multiple genes within a single cell. Current gene editing techniques that require different protein enzymes for each genetic modification may be limited in the number of edits they can make concurrently due to efficiency, cytotoxicity and/or manufacturing challenges. In contrast, CRISPR/Cas9 has the potential to efficiently make multiple edits using a single Cas9 protein and multiple small guide RNA molecules.

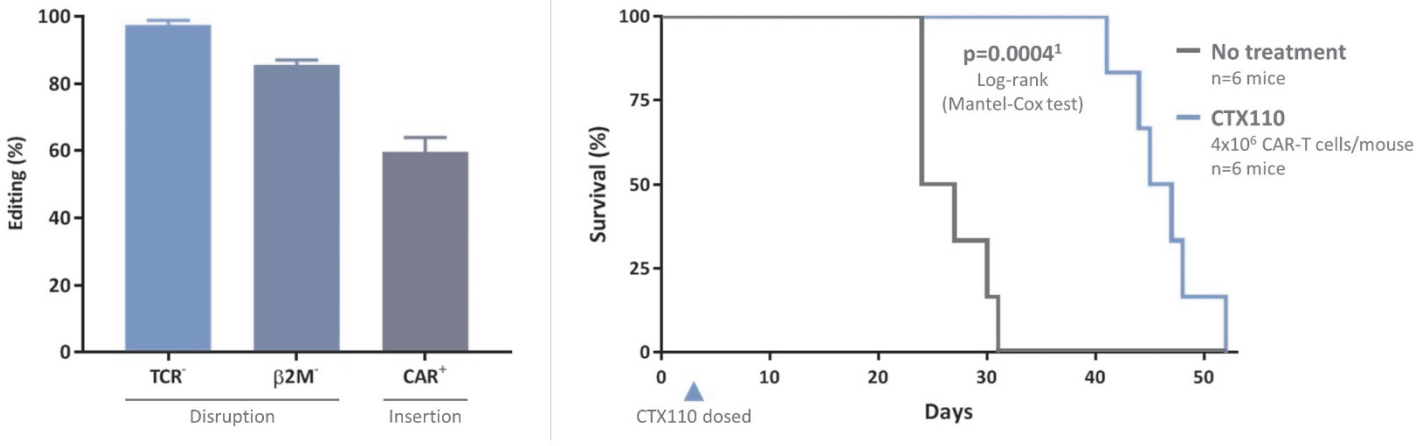
In our immuno-oncology cell therapies, we plan to use the multiplexing ability of CRISPR/Cas9 not only to enable allogeneic administration, but also to introduce additional genetic edits to improve the efficacy and safety profile of these product candidates. Such edits could include the removal of checkpoint inhibitors or introduction of safety elements. We continue to expand our multiplexing capabilities to help us realize the full potential of engineered cell therapy in immuno-oncology across all tumor types, including solid tumors. Given the important role we believe CRISPR/Cas9 will play in engineered cell therapy going forward we have thus far elected to retain full ownership of our immuno-oncology programs.

Our Lead Immuno-Oncology Product Candidate—CTX110

Our lead immuno-oncology product candidate, CTX110, is a healthy donor-derived allogeneic CAR-T cell therapy targeted toward CD19-positive malignancies, such as certain lymphomas and leukemias. A primary aim of CTX110 is to overcome the inefficiency and cost of creating a unique product for each patient in a tumor type by treating many different patients from a single batch, which we refer to as being an "off-the-shelf" therapy. To generate CTX110, we make three modifications to T cells taken from healthy donors using our gene-editing technology: (i) the T cell receptor, or TCR, is eliminated to reduce the risk of graft versus host disease, or GvHD, from the product candidate, (ii) a CD19-directed CAR is inserted site-specifically into the *TRAC* gene and (iii) the class I major histocompatibility complex, MHC I, is removed from the cell surface in order to improve the persistence of the CAR-T cells in an "off-the-shelf" setting. We believe this approach will have advantages over other allogeneic CAR-T products in development that semi-randomly insert the CAR using an integrating virus and do not include the MHC I knockout to increase persistence.

As shown in the figure below, we have demonstrated the ability to perform the edits necessary to generate CTX110 at high efficiency, and that in preclinical testing CTX110 prolonged the survival of mice with a CD19-positive xenograft tumor model that is comparable to what is seen with the current generation CAR-T products.

Efficient production of CTX110 via multiplexed editing and prolonged survival of CTX110-treated mice in a disseminated Nalm6 xenograft tumor model

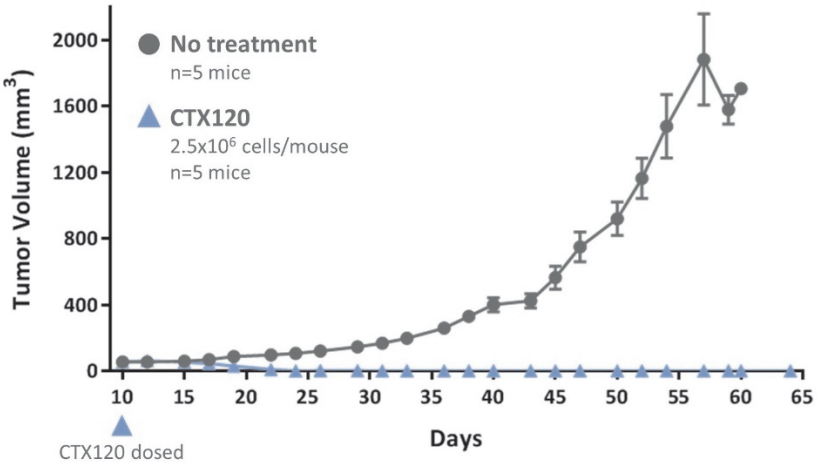


CTX120

Our second gene-edited allogeneic CAR-T cell product candidate, called CTX120 is targeted towards B-cell maturation antigen (BCMA) and is in development for the treatment of multiple myeloma. BCMA has attractive properties for CAR-T cell therapy, namely expression on the surface of B-lineage cells, especially the plasma cells involved in multiple myeloma, and absence from other tissues and cell types. As a result, BCMA has become a promising target for autologous CAR-T cell therapy. We believe an allogeneic approach may have distinct advantages over autologous CAR-T in multiple myeloma given the poor health of patient T cells following many lines of prior therapy.

To generate CTX120, we make the same three modifications to healthy-donor T cells as we do for CTX110 but insert a BCMA-specific CAR. CTX120 leverages many of the capabilities and reagents developed for CTX110, accelerating its path into development. As depicted in the figure below, in preclinical studies of CTX120, we observe complete elimination of a xenograft multiple myeloma tumor model in all mice treated with CTX120.

Elimination of a subcutaneous RPMI-8226 multiple myeloma model by CTX120

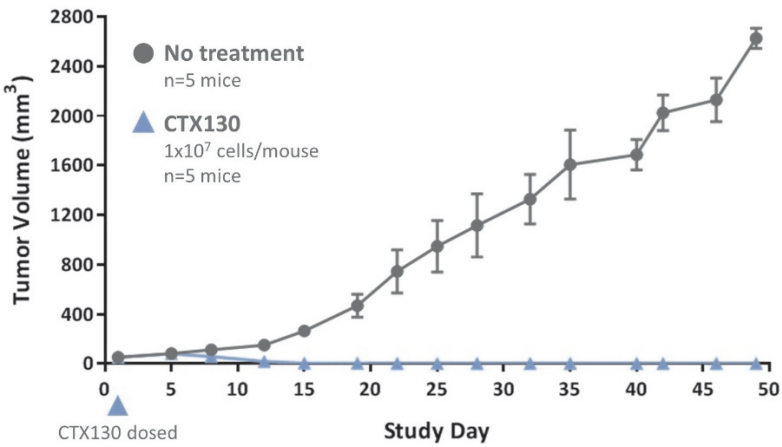


CTX130

Our third gene-edited allogeneic CAR-T cell product candidate, called CTX130, is targeted towards CD70 and is in development for the treatment of both solid tumors and hematologic malignancies. CD70 also shows properties that we believe make it a promising CAR-T cell target. Several cancers express CD70, including non-Hodgkin's lymphoma, renal cell carcinoma, glioblastoma and pancreatic, lung and ovarian cancers, while normal tissues do not express or show extremely limited expression of CD70. This target enables us to transition from hematological cancers, such as non-Hodgkin's lymphoma, to solid tumor cancers, such as renal cell carcinoma.

To generate CTX130, we plan to include additional edits beyond the three modifications used in CTX110 and CTX120. As shown in the figure below, in preclinical studies of CTX130, we observe complete elimination of a xenograft model of renal cell carcinoma in all mice treated with CTX130.

Elimination of a subcutaneous A498 renal cell carcinoma model by CTX130



Regenerative Medicine Programs

Regenerative medicine, or the use of stem cells to repair or replace tissue or organ function lost due to disease, damage or age, holds potential to treat both rare and common diseases. The field is approaching the point where clinical proofs of concept may begin to emerge. Most of these efforts use unmodified stem cells, and the potential to genetically engineer these cells via gene editing is large. We are pursuing gene-editing approaches to allow allogeneic use of stem cell-derived therapies by enabling immune evasion,

improving existing cell function and directing cell fate using CRISPR/Cas9. Our first major effort in this area is in diabetes together with our partner, ViaCyte.

ViaCyte Collaboration in Diabetes

Decades of clinical data with islet transplants indicate that beta-cell replacement approaches may offer a potentially curative benefit to patients with insulin-requiring diabetes. ViaCyte has pioneered the approach of generating pancreatic-lineage cells from stem cells and delivering them safely and efficiently to patients. PEC-Direct, ViaCyte's lead product candidate currently being evaluated in the clinic, uses a non-immunoprotective delivery device that permits direct vascularization of the cell therapy. This approach has the potential to deliver durable benefit; however, because the patient's immune system will identify these cells as foreign, PEC-Direct will require long-term immunosuppression to avoid rejection. As a result, PEC-Direct is being developed as a therapy for the subset of patients with type 1 diabetes at high risk for complications.

Our gene-editing technology offers the potential to protect the transplanted cells from the patient's immune system by *ex vivo* editing immune-modulatory genes within the stem cell line used to produce the pancreatic-lineage cells. We believe that the speed, specificity and multiplexing efficiency of CRISPR/Cas9 make our technology well suited to this task. We have established expertise in immune-evasive gene editing through our allogeneic CAR-T programs. The combination of ViaCyte's stem cell capabilities and our gene-editing capabilities has the potential to enable a beta-cell replacement product that may deliver durable benefit to patients without the need for immune suppression.

In Vivo and Other Genetic Disease Programs

We are also pursuing treatments for several genetic diseases beyond the hemoglobinopathies. For some of these indications, such as Hurler syndrome, we are taking an *ex vivo* approach. However, most of these programs involve *in vivo* gene editing, or delivery of a CRISPR/Cas9-based therapeutic directly to tissues within the human body. Our initial *in vivo* applications will leverage well-established delivery technologies, such as LNPs and AAV vectors.

We are pursuing liver diseases because delivery of nucleic acid therapies into the liver has been clinically established and validated delivery technologies are now available. We believe this proof of concept reduces the challenges associated with delivering CRISPR/Cas9-based therapeutics *in vivo* to the liver. Within the liver we are pursuing diseases that have well understood genetic linkages, such as Glycogen Storage Disease Type Ia, or GSDIa. Evidence suggests that correction of the mutant gene in only a small percentage of liver cells may have a significant therapeutic effect in this disease, which makes the gene correction strategy feasible.

In addition, we have initiated *in vivo* programs targeting diseases of organ systems outside the liver, such as Duchenne muscular dystrophy, or DMD, in the musculoskeletal system and cystic fibrosis, or CF, in the pulmonary system. In CF, we are working with Vertex, a global leader with extensive disease area expertise. We believe that our CRISPR/Cas9 gene editing technology is well suited to address DMD and CF, both of which have significant patient populations with high unmet medical need.

Glycogen Storage Disease Ia

GSDIa, also known as Von Gierke disease, is an autosomal recessive inborn error of glucose metabolism caused by a mutation in the G6PC gene, which encodes the glucose-6-phosphatase protein, or G6Pase. In patients with GSDIa, the lack of G6Pase prevents the release of glucose from the liver, resulting in accumulation of a large chain form of glucose known as glycogen. The inability of patients with GSDIa to regulate glucose levels leads to hypoglycemia, or low blood glucose, and high levels of lactic acid when patients are not eating, requiring patients to adhere to burdensome dietary regimes. GSDIa patients also face long-term risks such as growth delay, neuropathy and kidney stones. Additionally, due to the accumulation of glycogen in the liver, 70% to 80% of patients over 25 years of age will develop hepatocellular adenomas, a type of non-cancerous growth in the liver, of which approximately 10% will progress to hepatocellular carcinoma, a potentially fatal liver cancer. There are approximately 1,000 new cases of GSDIa per year worldwide.

There are currently no disease-modifying treatment options for patients with GSDIa. Any disruption in carbohydrate delivery may lead to low blood sugar levels, which can cause life-threatening consequences including seizure, coma and death. To minimize the risk of acute complications, patients are required to adhere to highly burdensome, lifelong dietary regimens such as overnight administration of uncooked cornstarch or a slow-release carbohydrate product such as Glycosade. These regimens have a high rate of non-compliance, leading to increased risk of serious long-term complications.

We are developing a CRISPR/Cas9 product candidate to correct the mutation in GSDIa patients. Animal model experiments have demonstrated that the addition of functional copies of the G6PC gene can correct the deficiency of G6Pase protein in GSDIa and that as little as 3% of normal levels of G6Pase can restore the equilibrium of glucose and glycogen in the bloodstream and liver. Our

approach is to correct the G6PC gene directly in its native location. We believe this direct gene correction will result in appropriate expression of the G6Pase protein. Other methods rely on adding copies of the gene through viral delivery methods, which we believe may lead to overexpression of the G6Pase protein and ineffective control of glucose levels.

Duchenne Muscular Dystrophy

DMD is an X-linked recessive genetic disease caused by a mutation in the dystrophin gene, which results in a lack of the dystrophin protein, a protein that plays a key structural role in muscle fiber function. The absence of dystrophin in muscle cells leads to significant cell damage and ultimately causes muscle cell death and fibrosis. DMD is characterized by muscle degeneration, loss of mobility and premature death, and is among the most prevalent severe genetic diseases, occurring in one in 3,300 male births worldwide. There is also a related form of muscular dystrophy called Becker muscular dystrophy, or BMD, which is also caused by mutations in the dystrophin gene. However, unlike DMD, the mutations in BMD result in the loss of certain exons or regions of the gene and can lead to an abnormal version of dystrophin that retains some function. As a result, BMD patients have milder symptoms than DMD patients.

There is currently one approved disease-modifying therapy in the United States for the treatment of DMD in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of the population with DMD. This therapy involves the use of oligonucleotides to promote exon skipping over the mutations that otherwise would result in truncated dystrophin synthesis. While exon skipping has demonstrated promising results in limited settings, larger clinical trials of this approach have suggested only modest efficacy. In addition, delivering sufficient levels of oligonucleotides requires repeated administration and presents challenges to treating DMD.

Our approach to treating DMD is to deliver CRISPR/Cas9 directly to muscle cells in patients to delete the defective exon in the dystrophin gene. The goal of this approach is to allow the gene to regain some functional capacity and produce enough dystrophin protein to diminish the more severe symptoms of DMD to resemble the milder form of the disease known as BMD. We believe that currently available technology can deliver the CRISPR/Cas9 into muscle cells, and together with the relatively high efficiency of exon deletion using the CRISPR/Cas9 system, we will be able to move this program into clinical testing. Prior studies in mice and humans have indicated that dystrophin levels as low as 4 to 15% of normal are sufficient to ameliorate symptoms, suggesting that even a partial restoration of dystrophin levels would be therapeutically beneficial.

Cystic Fibrosis

CF is a progressive disease caused by mutations in the cystic fibrosis transmembrane regulator, or CFTR, gene resulting in the loss or reduced function of the CFTR protein. Although there are several different mutations associated with CF, approximately 70% of CF patients have the same mutation at codon 508 of the CFTR gene. Patients with CF develop thick mucus in vital organs, particularly in the lungs, pancreas and gastrointestinal tract. As a result, CF patients experience chronic severe respiratory infections, chronic lung inflammation, poor absorption of nutrients, progressive respiratory failure and early mortality.

CF is an orphan disease that is estimated to effect more than 70,000 patients in the United States and Europe. The median age of death from CF in the United States was 31 years in 2017, with most deaths resulting from respiratory failure. CF patients require lifelong treatment with multiple daily medications and hours of self-care. They often require frequent hospitalizations and sometimes even lung transplantation, which can prolong survival but is not curative.

Studies have shown that as little as 10% of normal CFTR function can ameliorate disease symptoms. Our approach is focused on using our gene-editing technology to correct mutations in the CFTR gene. Together with our collaboration partner Vertex, we believe that we will be able to deliver CRISPR/Cas9 to the lung and correct this mutation sufficiently to improve symptoms in patients with CF.

Hurler Syndrome

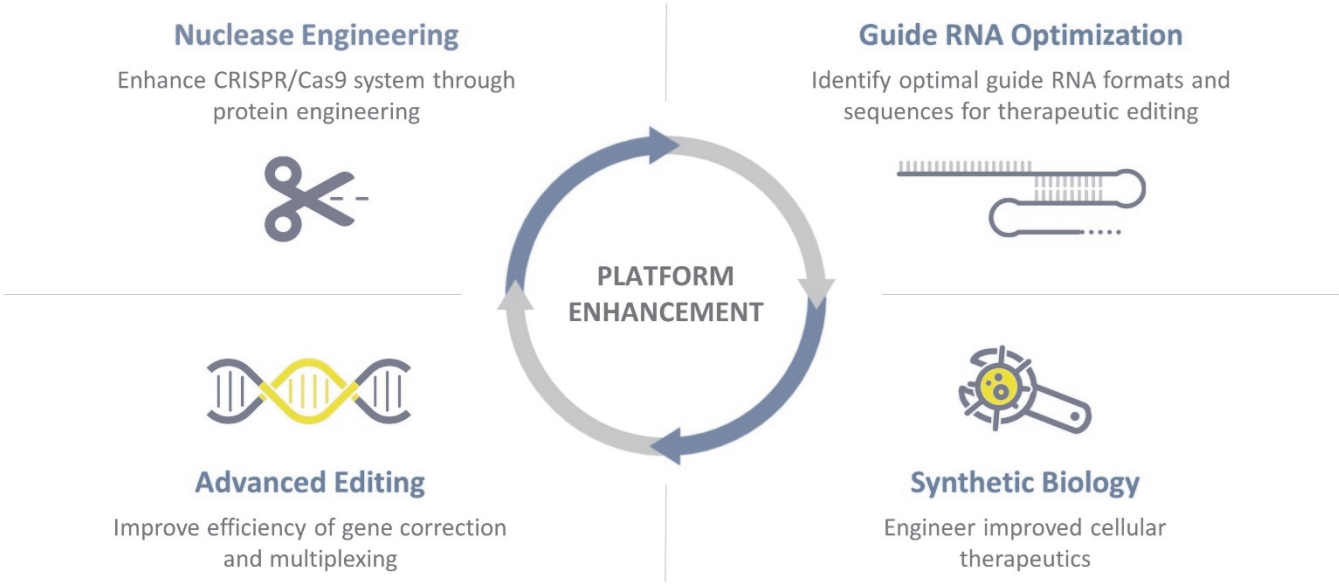
Hurler syndrome is a type of mucopolysaccharide disease caused by a defective IDUA gene. The IDUA gene is responsible for encoding alpha-L-iduronidase, an enzyme that breaks down large molecules called glycosaminoglycans, or GAGs, in the lysosomes of cells. A defective IDUA gene results in a lack of alpha-L-iduronidase which leads to an accumulation of GAGs and results in cellular dysfunction and severe clinical abnormalities. Patients with Hurler syndrome have a broad spectrum of clinical problems including skeletal abnormalities, enlarged livers and spleens, and severe intellectual disability due to a lack of this enzyme in the brain. Most patients experience a decline in intellectual development and often lose both vision and hearing as the disease progresses. Without treatment, the average age at death is five years, and nearly all patients die by the age of ten. The worldwide incidence of Hurler syndrome is approximately one in 100,000 births.

There are two common approaches to treating mucopolysaccharide diseases: enzyme replacement therapy, or ERT, and allo-HSCT. ERT does not adequately address the symptoms of Hurler syndrome because it cannot cross the blood-brain barrier to address the severe neurologic symptoms associated with this disease. While allo-HSCT can be effective in treating the disease, it is associated with significant morbidity and mortality, and not all patients are able to find suitable donors. Even when a match is found, the delay between diagnosis and treatment often results in significant irreversible disease progression.

Our approach is to introduce a functional copy of the IDUA gene into a patient's own hematopoietic cells using *ex vivo* CRISPR/Cas9 gene editing, before returning them to the patient. We believe that using a patient's own cells rather than those from a donor will eliminate a potentially lengthy search for an appropriate donor, allowing us to intervene at an earlier point and avoid the significant risks associated with allo-HSCT.

Further Unlocking the Potential of Our CRISPR/Cas9 Platform

We are working to optimize our CRISPR/Cas9 platform. Our key areas of focus are described below.



Nuclease Engineering

The Cas9 nucleases found in nature are highly efficient and specific. We believe that for many gene-editing applications, the naturally occurring Cas9 variants have all the properties required to support an effective therapeutic. However, we also see potential in certain disease areas and organ systems where modified versions of Cas9 may be more effective, and we are working internally and through our external collaborations to engineer Cas9.

Our research and development efforts seek to enhance several characteristics of Cas9, including size, specificity, immunogenicity and ability to support different types of editing strategies. We believe that the process of optimizing these different parameters may yield novel Cas9 versions with different properties, each of which may be best suited to a certain disease area or type of genetic editing.

Guide RNA Optimization

Selecting the sequence for guide RNAs is a critical step in the process of designing our product candidates. Once we have chosen a gene editing strategy, we seek to identify guide RNAs that will perform the desired edit with high efficiency and with undetectable or extremely low or off-target cutting. While computational models can predict efficiency and off-target effects with reasonable accuracy, we believe that a combination of computation and experimental approaches is necessary to reliably select the best possible guide RNAs.

Our guide RNA selection process combines bioinformatics and experimental assays to enable the screening of large numbers of guide RNAs in each experiment. This process starts with proprietary bioinformatics algorithms that select a large pool of guide RNAs that are predicted to have desired properties. These guides are then tested for target site cutting efficiency using a high-throughput

screening platform in a model cell line. The most efficient guides are then put through two screening processes for possible off-target effects. First, bioinformatics algorithms are used to identify the 10 to 20 sites in the genome that are most likely to show off-target effects, and these sites are examined through high-throughput assays for empirical off-target cutting. Second, homology-independent screening is performed to identify any potential off-target cutting, even at unpredicted locations. Finally, a small subset of guides with the highest efficiency and lowest off-target potential are tested in the cell type of therapeutic interest before choosing a lead guide or guides for our program.

Advanced Editing

While gene correction is achievable today using CRISPR/Cas9, it is more difficult and has lower efficacy than the more straightforward gene disruption strategy. Our initial gene correction programs target diseases in which therapeutic efficacy can be achieved through correction of only a small percentage of cells, while other potential indications may require correction of a significantly higher percentage of cells. We are working with our collaborators to increase the efficiency of gene correction to facilitate the potential treatment of these additional indications.

A central focus of our development efforts is to optimize the correction rates in cell types where rates of correction are typically low. Some of this optimization is being done internally, to test the influence of different parameters of the CRISPR/Cas9 system on correction efficiency. We are also collaborating more broadly with leaders in the DNA repair field, to explore other approaches to optimize correction rates.

We are also focused on expanding our ability to perform multiple edits simultaneously. In contrast to other gene editing technologies, which require extensive protein engineering and an additional construct for each new genetic target, CRISPR/Cas9 only requires a new guide RNA using simple Watson-Crick base pairing to target a new genetic locus. As a result, one can easily perform many edits at once using CRISPR/Cas9, a process known as multiplexing. Multiplexing holds promise in cell therapies, where making several modifications may lead to a safer and more efficacious therapy. Our research efforts in this area emphasize developing strategies to keep editing rates high while multiplexing without increasing the risk of off-target activity.

Synthetic Biology

The application of engineering principles to biological systems, broadly known as synthetic biology, could facilitate the development of improved cellular therapeutics. Novel strategies and tools in this area, such genetic circuits to regulate gene expression based on Boolean logic, may allow us to control specific cellular activity, such as the secretion of a protein, in response to selected input, such as an administered small molecule or a marker sensed on a cell surface. Synthetic biology holds promise when combined with CRISPR/Cas9 gene editing because CRISPR/Cas9 enables the precise engineering of such circuits into the genomes of cell therapies in order to improve their therapeutic properties. Given this potential, we have active efforts to develop and test such synthetic biology tools for incorporation into future immuno-oncology and regenerative medicine cell therapies.

Strategic Partnerships and Collaborations

We intend to develop CRISPR/Cas9-based therapeutics both independently and in collaboration with current and potential future corporate partners. We view strategic partnerships as a core component of our strategy, allowing us to access capabilities and resources in support of our therapeutic programs. We have established three broad strategic partnerships – a research collaboration with Vertex, a joint venture with Bayer and a research collaboration with ViaCyte – to develop gene-editing-based therapeutics in specific disease areas.

Under our agreement with Bayer, we established Casebia, a joint venture in which we and Bayer are equal owners. We and Bayer intend for Casebia to largely focus on more challenging *in vivo* therapeutic areas in larger patient populations, and to invest resources in optimizing the platform and delivery technologies for *in vivo* delivery. Through our agreement, we will have access to technology enhancements developed or obtained by Casebia for the benefit of our other wholly owned programs.

Our agreement with Vertex is a two-part collaboration. We granted Vertex an option to co-develop and co-commercialize rights to the hemoglobinopathies program and options to license certain other programs with the potential to receive milestone payments and royalties. Since signing the original agreement, Vertex has exercised their option to co-develop and co-commercialize the hemoglobinopathies program for which net profits and losses, as applicable, will be shared equally by the parties.

Under our collaboration agreement with ViaCyte, we and ViaCyte will jointly seek to develop an immune-evasive stem cell line to enable an allogeneic stem-cell derived beta cell replacement product. Upon successful completion of these studies and identification of a product candidate, we and ViaCyte will jointly assume responsibility for further development and commercialization worldwide.

Enabling Technologies

In support of our lead *ex vivo* programs, we have entered into a commercial license agreement with MaxCyte Incorporated ("MaxCyte"). The license provides CRISPR and Casebia a non-exclusive commercial-use right to MaxCyte's cell engineering platform to develop CRISPR/Cas9-based therapies for hemoglobin-related diseases and severe combined immunodeficiency. Our lead program, CTX001, utilizes MaxCyte's Flow Electroporation™ Technology to deliver CRISPR/Cas9 components to hematopoietic stem cells. In November 2018, we expanded our existing relationship with MaxCyte to deploy MaxCyte's Flow Electroporation™ Technology to develop CRISPR/Cas9-based therapies in immuno-oncology.

We have also formed several collaborations to support our *in vivo* programs. Together with Casebia, we have a collaboration with CureVac AG ("CureVac") to develop novel Cas9 mRNA constructs with improved properties for gene editing in the liver, such as increased potency, decreased duration of expression and reduced potential for immunogenicity. As part of the collaboration, CureVac will provide mRNA manufacturing through clinical development and commercialization.

We have also entered into a development and option agreement with StrideBio LLC ("StrideBio") to develop novel AAV vectors for *in vivo* gene editing applications. Under the agreement, StrideBio will use its proprietary structure-guided evolution platform to develop AAV vectors with improved properties, such as tissue specificity and reduced susceptibility to immune responses. Under this agreement we have the option to exclusively license AAV vectors with desired properties for certain of our *in vivo* programs. In February 2019, we expanded our existing relationship with StrideBio to develop AAV vectors for additional undisclosed applications.

We also entered into a multi-year research collaboration and license agreement with ProBioGen AG ("ProBioGen"), focused on the development of novel *in vivo* delivery modalities for CRISPR/Cas9 leveraging ProBioGen's existing technology and expertise. The collaboration includes a license option for CRISPR Therapeutics upon successful completion of the research goals.

Additionally, we have access to non-viral delivery technology through an exclusive license from the Massachusetts Institute of Technology to a family of LNP technologies developed in the lab of Dr. Daniel G. Anderson, a scientific founder and advisory board member of CRISPR Therapeutics.

Academic and Discovery Collaborations

We have a two-year research collaboration and license option agreement with Massachusetts General Hospital Cancer Center, or MGHCC, to develop novel T cell therapies for cancer. Marcela V. Maus, MD, PhD, Director of the Cellular Immunotherapy Program at MGHCC and Assistant Professor of Medicine at Harvard Medical School, will lead the scientific work at MGHCC. The research will involve using CRISPR/Cas9 gene editing to improve upon current T cell therapies in development, ultimately addressing unmet needs in both hematologic and solid tumors.

Also in the immuno-oncology space, we have a research collaboration with Neon Therapeutics, an immuno-oncology company developing neoantigen-based therapeutic vaccines and T cell therapies to treat cancer. The collaboration combines our respective proprietary technologies to explore the development of novel T cell therapies.

We and our collaborators at the University of Florida, or UF, have received a two-year grant from Target ALS Foundation to support preclinical discovery and validation of CRISPR/Cas9-based therapeutic approaches directed to ALS and frontotemporal dementia. We will collaborate with Dr. Laura Ranum and Dr. Eric Wang at UF to test CRISPR/Cas9 gene editing strategies in animal models of the disease.

We also received the Kyle Bryant Translational Research Award from Friedreich's Ataxia Research Alliance, or FARA, a non-profit organization that is focused on curing Friedreich's Ataxia, or FA. The grant will fund research on *in vivo* CRISPR/Cas9-based gene-editing approaches to treat FA, which we will conduct in collaboration with Dr. Marek Napierala at University of Alabama at Birmingham.

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions and improvements that we believe are commercially important to our business by seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties, that cover our gene-editing technology, existing and planned therapeutic programs. We also rely on trade secret protection and confidentiality agreements to protect our proprietary technologies and know-how to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection, as well as continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of gene editing. We additionally rely

on trademark protection, copyright protection and regulatory protection available via orphan drug designations, data exclusivity, market exclusivity, and patent term extensions. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for our technology, our ability to defend and enforce our intellectual property rights and our ability to operate without infringing any valid and enforceable patents and proprietary rights of third parties.

In-Licensed Intellectual Property from Dr. Charpentier

In April 2014, pursuant to an exclusive license with Dr. Emmanuelle Charpentier, we licensed certain rights to a worldwide patent portfolio which covers various aspects of our genome editing platform technology including, for example, compositions of matter, including additional CRISPR/TRACR/Cas9 complexes, and methods of use, including their use in targeting or cutting DNA. We refer to this worldwide patent portfolio as the "Patent Portfolio". This license is limited to therapeutic products such as pharmaceuticals and biologics and any associated companion diagnostics, for the treatment or prevention of human diseases, disorders, or conditions. For further information about this license, please see "Business – CRISPR License with Dr. Emmanuelle Charpentier."

In addition to Dr. Emmanuelle Charpentier, the Patent Portfolio has named inventors who assigned their rights either to the Regents of the University of California, or California, or the University of Vienna, or Vienna. California's rights are subject to certain overriding obligations to the sponsors of its research, including the Howard Hughes Medical Institute and the U.S. Government. Caribou Biosciences, or Caribou, had reported that it had an exclusive license to patent rights from California and Vienna, subject to a retained right to allow non-profit entities to use the inventions for research and educational purposes. Intellia Therapeutics, Inc., or Intellia, had reported that it had an exclusive license to such rights from Caribou in certain fields.

On January 11, 2016, the U.S. Patent and Trademark Office (USPTO), declared an interference between one of the pending U.S. patent applications included in the Patent Portfolio and twelve issued U.S. patents owned jointly by the Broad Institute and Massachusetts Institute of Technology and, in some instances, the President and Fellows of Harvard College, which we refer to individually and collectively as Broad. The interference was redeclared on March 17, 2016 to add a U.S. patent application owned by Broad. An interference is a proceeding conducted at the USPTO by the Patent Trial and Appeal Board (PTAB), to determine priority of invention of subject matter claimed by at least two parties. Following motions by the parties and other procedural matters, the PTAB concluded in February 2017that the declared interference should be discontinued without deciding which party was the first to invent. In its decision, the PTAB concluded that the claim sets presented by the two parties were considered patentably distinct from each other because the involved CVC patent application's claims were broader in scope in that they were not restricted to use in eukaryotic cells, whereas Broad's claims were so limited. In April 2017, CVC appealed the PTAB decision to the U.S. Court of Appeals for the Federal Circuit (Federal Circuit). In the appeal, CVC asked the court to review and reverse the PTAB's February 2017 decision, which terminated the interference without determining which inventors first invented the use of the CRISPR/Cas9 genome editing technology in eukaryotic cells. The Federal Circuit conducted a hearing on the appeal on April 30, 2018, and on September 10, 2018, affirmed the PTAB's decision to terminate the interference proceeding. As a result of the Federal Circuit's decision, U.S. Serial No. 13/842,859, which was previously considered allowable, was released from the interference and returned to the USPTO.

We expect CVC will continue to prosecute patent claims covering inventions included in the Patent Portfolio, which could also result in allowable or issued patents in the United States, Europe or other foreign jurisdictions. The patents and patent applications within the Patent Portfolio are, or may in the future be, subject to further intellectual property proceedings and disputes in the U.S. CVC, Broad or other parties could seek a new interference involving some or all of the technology in the Patent Portfolio, and any existing or new patents could be the subject of other challenges to their validity of enforceability. If an interference was declared, either party could appeal an adverse decision to the Federal Circuit. In any case, it may be years before there is a final determination on priority. Pursuant to the terms of the license agreement with Dr. Charpentier, we are responsible for covering or reimbursing Dr. Charpentier's patent prosecution, defense and related costs associated with our in-licensed technology.

The patents and patent applications within the Patent Portfolio are, or may in the future be, involved in proceedings similar to interferences or priority disputes in Europe or other foreign jurisdictions. For example, the Opposition Division has initiated opposition proceedings against European Patent Nos. EP 2,800,811 B1 and EP 3,241,902 B1. The EPO opposition proceedings may involve issues including, but not limited to, procedural formalities related to filing the European patent application, priority, and the patentability of the involved claims. We cannot be certain which of these results, if any, will actually occur or at what time, and the effects that any such results may have on us and our intellectual property position are currently unknown.

For further information regarding risks regarding the interference and patent rights held by third parties, please see "Risk Factors—Risks Related to Intellectual Property."

On December 15, 2016, we entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement, or the IMA, with California, Vienna, Dr. Charpentier, Intellia, Caribou, ERS Genomics Ltd., or ERS, and TRACR. Under the IMA, California and Vienna retroactively consent to Dr. Charpentier's licensing of her rights to the CRISPR/Cas9

intellectual property, pursuant to our license with Dr. Charpentier, to us, our wholly-owned subsidiary TRACR, and ERS, in the United States and globally. The IMA also provides retroactive consent of co-owners to sublicenses granted by us, TRACR and other licensees, prospective consent to sublicenses they may grant in future, retroactive approval of prior assignments by certain 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 and with respect to certain adverse claimants of the CRISPR/Cas9 intellectual property. Unless earlier terminated by the parties, the IMA will continue in effect until the later of the last expiration date of the patents underlying the gene-editing technology, or the date on which the last underlying patent application is abandoned. For further information regarding the effects of joint ownership in the United States and in other jurisdictions worldwide, please see "Risk Factors – *The Intellectual Property That Protects Our Core Gene Editing Technology Is Jointly Owned, And Our License Is From Only One Of The Joint Owners, Materially Limiting Our Rights In The United States And In Other Jurisdictions*."

CRISPR-Owned Intellectual Property

In addition to the Patent Portfolio, we have a broad intellectual property estate that includes numerous patent families covering key aspects of our CRISPR/Cas9 technologies and development programs which is intended to provide multiple layers of protection. These patent families encompass filings covering our development programs (such as composition of matter, method of use, manufacturing processes, dosing and formulations), the use and improvement modifications of CRISPR/Cas9 systems for gene editing (such as improvements to component systems including nucleases and single or modified guide RNAs), technologies for delivering protein/nucleic acid complexes and RNA into cells (such as improved viral vector systems and self-inactivating systems), and technology relevant to stem cell-based therapies.

Overall, our intellectual property estate includes over 40 active patent families and approximately 25 granted or allowed patents in the United States, United Kingdom, Europe, Japan, China, Ukraine, New Zealand, Singapore, Australia, Mexico, Tunisia, Hong Kong, Israel and South Africa, and pending patent applications in the United States, Europe, Australia, Canada, China, Japan, Mexico and other selected countries in Central America, South America, the Middle East, Asia and Africa. The granted patents and any other patents that may ultimately issue from these patent families are expected to expire starting in 2033, not including any applicable patent term extensions.

Our US trademark estate consists of 9 pending applications for CRISPR COLLECTIVE, CRISPR THERAPEUTICS, CTX001, CTX101, CTX110, CTX120, CTX130, the CRISPR COLLECTIVE logo, and the CRISPR THERAPEUTICS logo. Our international trademark estate consists of 15 pending applications and 3 International Registrations. We have pending applications for CRISPR COLLECTIVE and CRISPR THERAPEUTICS in the EU, Switzerland, and UK. We also have International Registrations for CTX001, CTX101, and the CRISPR THERAPEUTICS logo designating the EU, Switzerland, and UK.

Patent Assignment Agreement

In November 2014, we entered into a patent assignment agreement with Dr. Emmanuelle Charpentier, Dr. Ines Fonfara and Vienna, or the Patent Assignment Agreement. Under the Patent Assignment Agreement, Dr. Charpentier, Dr. Fonfara and Vienna assigned to us all rights to a family of patent applications relating to certain compositions of matter, including additional CRISPR/TRACR/Cas9 complexes, and methods of use, including their use in targeting or cutting DNA.

As consideration for the patent rights assigned to us, we agreed to pay an upfront payment, milestone payments beginning with the filing of a U.S. Investigational New Drug application or its equivalent in another country, a minimum annual royalty, a low single-digit royalty on net sales of products whose manufacture, use, sale, or importation is covered by the assigned patent rights, and a low single-digit percentage of licensing revenues.

We are obliged to use commercially reasonable efforts to obtain regulatory approval to market a product whose manufacture, use, sale, or importation is covered by the assigned patent rights, including but not limited to an obligation to use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country) by November 2021.

License Agreements

CRISPR License With Dr. Emmanuelle Charpentier

In April 2014, we entered into a license agreement, or the Charpentier License Agreement, with Dr. Emmanuelle Charpentier, one of our co-founders, pursuant to which we received an exclusive license under Dr. Charpentier's joint ownership interest in the Patent Portfolio, to research, develop and commercialize therapeutic products such as pharmaceuticals or biological preparations, and any associated companion diagnostics, for the treatment or prevention of human diseases, disorders, or conditions, other than hemoglobinopathies, which we refer to as the CRISPR Field. The license is exclusive, even as to Dr. Charpentier, except that she retains a non-transferable right to use the technology for her own research purposes and in research collaborations with academic and non-profit partners. The exclusive license is granted only under Dr. Charpentier's interest in the patent applications and the exclusivity

is not granted under any other joint owner's interest. Additionally, the Charpentier License Agreement granted us an exclusive, worldwide, royalty-free sublicense, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic products relating to the CRISPR Field which incorporate any intellectual property that TRACR Hematology Ltd., our wholly-owned subsidiary, or TRACR, develops under its license with Dr. Charpentier. In turn, we granted to Dr. Charpentier an exclusive license with the obligation to sublicense to TRACR any intellectual property we develop under the license with Dr. Charpentier for treatment and prevention of hemoglobinopathies in humans, including, without limitation, sickle cell disease and thalassemia.

Under the terms of the Charpentier License Agreement, as consideration for the license, Dr. Charpentier received a technology transfer fee, an immaterial annual maintenance fee, immaterial milestone payments that will be due after the initiation of clinical trials, a low single digit percentage royalty on net sales of licensed products, and a low single digit percentage royalties of sublicensing revenue. We are obligated to use commercially reasonable efforts to obtain regulatory approval to market a licensed therapeutic product. CRISPR must use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country for a therapeutic product in the CRISPR field) by April 2021. In addition, CRISPR must file a U.S. Investigational New Drug application (or its equivalent in a major market country) for a therapeutic product in the CRISPR field by April 2024.

Unless terminated earlier, the term of the Charpentier License Agreement will expire on a country-by-country basis, upon the expiration of the last to expire valid claim of the Patent Portfolio in such country. We have the right to terminate the agreement at will upon 60 days' written notice to Dr. Charpentier. We and Dr. Charpentier may terminate the agreement upon 90 days' notice in the event of a material breach by the other party, which is not cured during the 90-day notice period. Dr. Charpentier may terminate the license agreement immediately if we challenge the enforceability, validity, or scope of any Patent Portfolio.

TRACR License With Dr. Emmanuelle Charpentier

In April 2014, concurrently with our license agreement with Dr. Emmanuelle Charpentier, TRACR Hematology Ltd., our wholly- owned subsidiary, entered into a license agreement, or the TRACR License Agreement, with Dr. Charpentier, a minority shareholder of TRACR, under the Patent Portfolio. Pursuant to the TRACR License Agreement, TRACR was granted an exclusive, worldwide, royalty-bearing license, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic and diagnostic products for the treatment and prevention of hemoglobinopathies in humans, including sickle cell disease and thalassemia, or the TRACR Field. TRACR also received a non-exclusive, worldwide, royalty-free license, including the right to sublicense, to carry out internal pharmaceutical research for therapeutic products outside of the TRACR Field and an exclusive, worldwide, royalty-free sublicense, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic products relating to the TRACR Field which incorporate any intellectual property that CRISPR develops under its license with Dr. Charpentier. In turn, TRACR granted to Dr. Charpentier an exclusive license to sublicense to CRISPR any intellectual property that TRACR develops under the license with Dr. Charpentier for use in the CRISPR Field.

TRACR is obligated to use commercially reasonable efforts to research, develop, and commercialize at least one therapeutic product for the prevention or treatment of human disease under the license agreement. TRACR must use commercially reasonable efforts to file a U.S. Investigational New Drug application (or its equivalent in a major market country) for a therapeutic product in the TRACR field by April 2021. In addition, TRACR must file a U.S. Investigational New Drug application (or its equivalent in a major market country) for a therapeutic product in the TRACR field by April 2024. TRACR is solely responsible for all clinical, regulatory and development costs.

Under the TRACR License Agreement, Dr. Emmanuelle Charpentier is entitled to receive immaterial clinical and regulatory milestone payments per product that TRACR commercializes. TRACR is also required to pay Dr. Charpentier low single digit percentage royalties on the net sales of any approved therapeutic or diagnostic products, made by it, its affiliates, or its sublicensees and low single-digit percentage royalties on sublicensing revenue.

Unless terminated earlier, the term of the license agreement will expire on a country-by-country basis, upon the expiration of the last to expire valid claim of the Patent Portfolio in such country. TRACR has the right to terminate the agreement at will upon 60 days' written notice to Dr. Emmanuelle Charpentier. TRACR and Dr. Charpentier may terminate the agreement upon 90 days' notice in the event of a material breach by the other party, which is not cured during the 90-day notice period. Dr. Charpentier may terminate the license agreement immediately if TRACR challenges the enforceability, validity, or scope of any Patent Right.

Bayer Joint Venture

In December 2015, we entered into a Joint Venture Agreement, or the JV Agreement, with Bayer HealthCare LLC, or Bayer HealthCare, to create Casebia Therapeutics LLP, or Casebia, to discover, develop and commercialize new therapeutics for genetically linked diseases, including blood disorders, blindness and heart disease. At the closing of the transactions contemplated by the JV

Agreement in March 2016, or the Closing, we contributed $0.1 million to Casebia and we and certain of our affiliates entered into an intellectual property contribution agreement with Casebia, or the CRISPR IP Contribution Agreement, as discussed below, exclusively licensing our CRISPR/Cas technology to Casebia for the purpose of developing and commercializing therapeutic products in certain specified fields, or the Casebia Fields. Bayer HealthCare contributed an initial amount of $45 million at the Closing to Casebia and is committed to contribute up to an additional $255 million in additional funds over time to fund the operations of Casebia, subject to the conditions and procedures discussed below. We and Bayer HealthCare each hold a 50%, non-transferable interest in Casebia.

Casebia's initial focus will be within the areas of hematology, ophthalmology and cardiology and autoimmune diseases, in addition to select indications related to other sensory organs and metabolic diseases. Within these areas of focus, we and Bayer HealthCare each have exclusive rights to specified disease indications, the CRISPR Field and Bayer Field, respectively, as discussed below.

Governance

In November of 2016, Casebia appointed James Burns as chief executive officer, or CEO, of Casebia, replacing Axel Bouchon, the head of LifeScience Center of Bayer AG, who was serving as interim CEO. Dr. Burns also joined the Casebia Board as a non-voting member. Casebia is generally governed by a management board, or the Management Board, which is comprised of four voting members, two of which are designated by us and two of which are designated by Bayer. We have designated Drs. Novak and Kulkarni to serve as our designees to the Management Board. Decisions of the Management Board are generally made by majority vote, with each member having one vote. Certain matters require the consent of Bayer HealthCare and us.

Budget and Funding

The JV Agreement sets forth the initial 24-month budget for Casebia, which will be revised by the Management Board on a yearly basis for the following 24 months. Bayer HealthCare, subject to certain conditions, is solely responsible for providing Casebia with the necessary additional funding as determined by the Management Board until the earlier of (i) its aggregate additional commitment amount of $255 million is fully funded, at which point all additional financing must be approved by the Management Board or (ii) the termination of the JV Agreement in accordance with its terms. Any additional funding beyond the amounts initially committed by Bayer HealthCare in the JV Agreement up to the $300 million aggregate commitment amount, whether for purposes of an acquisition or otherwise, will not affect or dilute our 50% interest in Casebia.

Non-Competition

During the term of the JV Agreement, neither we nor Bayer HealthCare, nor any of our respective affiliates, may develop, commercialize or otherwise exploit any competing product utilizing the CRISPR/Cas technology in any of the Casebia Fields unless, in the case of CRISPR or one of our affiliates, a target is the subject of a pre-existing license or an approved third-party agreement, or certain other excluded targets. In addition, in the event either we, Bayer HealthCare or a third party license a product candidate from Casebia pursuant to the Option Agreement discussed below, the non-licensing party or parties to the JV Agreement will be prohibited from developing, commercializing or otherwise exploiting any product utilizing CRISPR/Cas technology to target the same target as that of the licensed product candidate in any of the fields covered by such Option Agreement, so long as the licensing party is clinically developing, commercializing or otherwise exploiting such licensed product candidate.

Furthermore, upon a termination by either party for specified breaches of the other party, the defaulting party will be prohibited from utilizing the CRISPR/Cas technology to develop, commercialize or otherwise exploit product candidates in the field of the terminating party which would be competitive with the terminating party, for a period of two years following such termination.

Termination

The JV Agreement can be terminated by Bayer HealthCare and us upon mutual written consent. Either party may terminate the JV Agreement in the event of specified breaches by the other party or in the event the other party becomes subject to specified bankruptcy, winding up or similar circumstances. Either party may also terminate upon a change of control of the other party, as defined in the JV Agreement. Bayer HealthCare also has the right to terminate in the event (i) we are not able to maintain the intellectual property rights licensed to Casebia pursuant to the CRISPR IP Contribution Agreement or (ii) we have not achieved preclinical proof of concept with a CRISPR/Cas9 product candidate in a specified period of time. The JV Agreement may also be terminated by either party if, subsequent to the time that Bayer HealthCare has funded its entire $300 million commitment, the Management Board is unable to approve and obtain sufficient funding, within the time specified in the JV Agreement, to continue Casebia's operations for the next 18 months.

Subject to certain exceptions, in the event of a termination, all Casebia owned patents, know-how and technology will be jointly owned by us and Bayer HealthCare, with the right to sublicense. Upon termination, subject to certain exceptions, Bayer HealthCare will receive an exclusive license to Casebia CRISPR/Cas technology for all non-human therapeutic uses in the Bayer Field and a non-exclusive license for human therapeutic uses. Upon such termination, we will receive an exclusive license to Casebia CRISPR/Cas technology in human therapeutic areas, other than in the Bayer Field, and a non-exclusive license for human therapeutic uses in the Bayer Field. Upon any termination, all rights licensed to Casebia pursuant to the CRISPR IP Contribution Agreement will terminate, except for any rights licensed to third parties or to a party who has exercised an option pursuant to the Option Agreement described below.

IP Contribution Agreement with Casebia

As part of our contribution to Casebia, in March 2016, we and certain of our affiliates entered into the CRISPR IP Contribution Agreement with Casebia. Pursuant to the CRISPR IP Contribution Agreement, we and certain of our affiliated entities granted Casebia an exclusive, worldwide, fully paid-up, royalty-free license, including the right to sublicense, to the use of our CRISPR/Cas technology to research, develop, produce, commercialize and sell products in the Casebia Fields. As partial consideration for the license, Casebia is required to pay us an aggregate amount of $35 million for a technology access fee, consisting of an upfront payment of $20 million, which was paid at the closing of the JV Agreement in March 2016, and another payment of $15 million when we obtain specified intellectual property rights relating to our gene-editing technology outside of the United States, which was paid in December 2016 upon the signing of the IMA. The CRISPR IP Contribution Agreement also contains license grants from Casebia to us to various forms of intellectual property developed or in-licensed by Casebia. The CRISPR IP Contribution Agreement will terminate simultaneously with the termination of the JV Agreement, subject to survival of certain licenses granted during the term, including licenses granted pursuant to an exercise of an option pursuant to the Option Agreement.

Option Agreement with Bayer

In connection with the Closing, in March 2016, we, Bayer HealthCare and Casebia entered into an Option Agreement. Pursuant to the Option Agreement, in the event the FDA accepts an IND submitted by Casebia for any product candidate it is developing, both we and Bayer HealthCare have the right to submit an offer to enter into a license with Casebia for the exclusive right to develop, manufacture and commercialize the product candidate in certain Casebia Fields. In addition, Casebia is allowed to receive and consider unsolicited third-party offers, and both we and Bayer HealthCare can require Casebia to seek third-party offers for the applicable product candidate. The Option Agreement sets forth the procedures the Management Board will follow when considering and voting on any offers as well as the considerations on how to value any offer.

Collaboration Agreement with Vertex

On October 26, 2015, we entered into a Strategic Collaboration, Option and License Agreement, or the Collaboration Agreement, with Vertex Pharmaceuticals, Incorporated and Vertex Pharmaceuticals (Europe) Limited, together, Vertex. Pursuant to the Collaboration Agreement, we agreed to provide technology and options to obtain licenses relating to our CRISPR/Cas technology to Vertex in exchange for a $75 million upfront payment. In connection with the Collaboration Agreement, Vertex also made a $30 million equity investment in us. Under the Collaboration Agreement, Vertex has the option to exclusively license treatments for up to six collaboration targets that emerge from the four-year research collaboration under certain of our platform and background intellectual property to develop, manufacture, commercialize, sell and use therapeutics directed to each such collaboration target. For any non-hemoglobinopathies targets in-licensed for development, Vertex will pay future development, regulatory and sales milestones of up to $420 million per target, as well as royalty payments in the single digits to low teens on future sales of a commercialized product candidate. The milestone and royalty payments are each subject to reduction under certain specified conditions set forth in the Collaboration Agreement. For these therapies, Vertex is solely responsible for all research, development, manufacturing and global commercialization activities. Matters relating to hemoglobinopathies targets our governed by the JDA we have with Vertex, as summarized below.

The initial focus of the Vertex collaboration will be to use CRISPR/Cas9 technology to discover and develop gene-based treatments for hemoglobinopathies and cystic fibrosis. Further discovery efforts focused on a specified number of other genetic targets will also be conducted under the Collaboration Agreement. We will be responsible for discovery activities, and the related expenses will be fully funded by Vertex. Under the Collaboration Agreement, we and Vertex have each agreed to certain exclusivity obligations with respect to targets subject to the Collaboration Agreement.

Either party can terminate the Collaboration Agreement upon the other party's material breach, subject to specified notice and cure provisions. Vertex also has the right to terminate the Collaboration Agreement for convenience at any time upon 90 days' written notice prior to any product receiving marketing approval and upon 270 days' notice after a product has received marketing approval. In the event we and Vertex make a filing under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, for a

collaboration target and such filing is not cleared within a specified time after such filing, the Collaboration Agreement will terminate with respect to that target. We may also terminate the Collaboration Agreement in the event Vertex challenges any of our patent rights.

Absent early termination, the Collaboration Agreement will continue until the expiration of the Vertex's payment obligations under the Collaboration Agreement. Upon termination, the targets that are not licensed by Vertex will be returned to us.

In connection with entering into the JDA on December 12, 2017, we and Vertex entered into Amendment No. 1 to the Collaboration Agreement, or the Amendment. The Amendment, among other things, modified certain definitions and provisions of the Collaboration Agreement to make them consistent with the JDA and clarified how many options are exercised (or deemed exercised) in connection with certain targets specified under the Collaboration Agreement. The Amendment also amended other provisions of the Collaboration Agreement, including the expiration terms of the Collaboration Agreement.

Joint Development Agreement with Vertex

On December 12, 2017, we entered into the JDA with Vertex. The initial focus of the JDA is for the development of CTX001 for beta thalassemia and SCD. In connection with entering into the JDA, we received a $7.0 million up-front payment from Vertex and are eligible for a one-time low seven-digit milestone payment upon the dosing of the second patient in a clinical trial with the initial product candidate. The net profits and net losses, as applicable, incurred under the JDA will be shared equally between us and Vertex.

The JDA includes, among other things, provisions relating to the following:

Governance. CRISPR and Vertex will form the following committees: (i) a joint steering committee to provide high-level oversight and decision making regarding the activities covered by the JDA, (ii) a joint development committee to provide oversight and decision making-making regarding development activities, (iii) a joint commercialization committee to provide oversight and decision-making regarding commercialization activities and (iv) a joint manufacturing committee to provide oversight and decision-making regarding manufacturing activities. Each of the committees will contain an equal number of representatives from each of CRISPR and Vertex.

Commercialization. The JDA provides that we will be the responsible for commercialization activities in the United States and Vertex will be responsible for commercialization activities outside of the United States.

Termination. Either party can terminate the JDA upon the other party's material breach, subject to specified notice and cure provisions, or, in the case of Vertex, in the event that we become subject to specified bankruptcy, winding up or similar circumstances. Either party may terminate the JDA in the event the other party commences or participates in any action or proceeding challenging the validity or enforceability of any patent that is licensed to such challenging party pursuant to the JDA. Vertex also has the right to terminate the JDA for convenience at any time after giving prior written notice.

If circumstances arise pursuant to which a party would have the right to terminate the JDA on account of an uncured material breach, such party may elect to keep the JDA in effect and cause such breaching party to be treated as if it had exercised its opt-out rights with respect to the products associated with such uncured material breach (described below) and the royalties payable to the breaching party would be reduced by a specified percentage.

Opt-Out Rights. Either party may opt of out of the development of a product candidate under the JDA after predetermined points in the development of the product candidate, on a candidate-by-candidate basis. In the event of such opt-out, the party opting-out will no longer share in the net profits and net losses associated with such product candidate and, instead, the opting out party will be entitled to high single to mid- teen percentage royalties on the net sales of such product, if commercialized.

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 qualified third-party organizations to produce or process bulk compounds, formulated compounds, viral vectors or engineered cells for IND-supporting activities and early stage clinical trials. We expect that commercial quantities of any compound, vector, or engineered cells that we may seek to develop will be manufactured in facilities and by processes that comply with FDA and other regulations. At the appropriate time in the product development process, we will determine whether to establish manufacturing facilities or continue to rely on third parties to manufacture commercial quantities of any products that we may successfully develop. Outside of the United States and Europe, where appropriate, we may elect in the future to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products. In certain instances, we may consider building our own commercial infrastructure.

As product candidates advance through our pipeline, our commercial plans may change. In particular, some of our research programs target potentially larger indications. Data, the size of the development programs, the size of the target market, the size of a commercial infrastructure and manufacturing needs may all influence our strategies in the United States, Europe and the rest of the world.

Competition

The biotechnology and pharmaceutical industries, including in the gene therapy and gene editing fields, are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on intellectual property and proprietary products. While we believe that our technology, development experience, and scientific knowledge provide us with competitive advantages, we currently face, and will continue to face, competition from many different sources, including major pharmaceutical, specialty pharmaceutical, and biotechnology companies, academic institutions and governmental agencies, and public and private research institutions. For any products that we may ultimately commercialize, not only will we compete with any existing therapies and those therapies currently in development, we will have to compete with new therapies that may become available in the future.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that utilize technologies encompassing genomic medicines to create therapies, including gene editing, gene therapy, and cell therapy. In addition, we compete with companies working to develop therapies in areas related to our specific research and development programs.

Our platform and product focus is on the development of therapies using CRISPR/Cas9 technology. Other companies developing CRISPR/Cas9 technology include Intellia Therapeutics and Editas Medicine.

There are also companies developing therapies using additional gene-editing technologies, such as TALENs, meganucleases, and zinc finger nucleases. These companies include Allogene Therapeutics, bluebird bio, Cellectis, Precision BioSciences, and Sangamo Therapeutics.

Additional companies are developing gene and cell therapy products more generally, including Abeona Therapeutics, Adverum Biotechnologies, Celgene, Fate Therapeutics, Gilead Sciences, Novartis Pharmaceuticals, Orchard Therapeutics, Poseida Therapeutics, REGENXBIO and Sarepta Therapeutics. In addition to competition from other gene-editing, gene, or cell therapies, any products that we develop may also face competition from other types of therapies, such as small molecule, antibody or protein therapies.

We may also face future competition from newly discovered gene editing technologies or new CRISPR-associated nucleases. While we believe that CRISPR/Cas9 will be highly effective for many therapeutic applications and are actively working to further enhance the technology, more efficient gene editing technologies may emerge. For example, publications by Feng Zhang, Ph.D., one of the founders of Editas Medicine, and others elucidated a different CRISPR-associated nuclease, Cpf1, which can also edit human DNA. Some have argued that Cpf1 is superior to Cas9 for certain applications. Multiple academic labs and companies have also published on other CRISPR-associated nuclease variants that can edit human DNA. In addition, new CRISPR-based technologies, such as base editing, may arise. These new technologies could have advantages over CRISPR/Cas9 gene editing in some applications. Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition.

In addition, many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety, convenience, and availability of reimbursement.

If our current programs are approved for the indications for which we are currently planning clinical trials, they may compete with other products currently under development, including gene editing, gene therapy, and cell therapy products. Competition with other related products currently under development may include competition for clinical trial sites, patient recruitment, and product sales.

In addition, due to the intense research and development taking place in the gene editing field, including by us and our competitors, the intellectual property landscape is in flux and highly competitive. There may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third party, intellectual property and proprietary rights in the future.

For example, on January 11, 2016, at our request, the USPTO declared an interference between one of the pending U.S. patent applications included in the Patent Portfolio and twelve issued U.S. patents, and subsequently added one U.S. patent application, owned by the Broad. The interference was redeclared on March 17, 2016 to add a U.S. patent application owned by Broad. . Following motions by the parties and other procedural matters, the PTAB concluded in February 2017 that the declared interference should be dismissed without deciding which party was the first to invent. In its decision, the PTAB concluded that the claim sets presented by the two parties were considered patentably distinct from each other because the involved CVC patent application's claims were broader in scope in that they were not restricted to use in eukaryotic cells, whereas Broad's claims were so limited. In April 2017, CVC appealed the PTAB decision to the Federal Circuit. In the appeal, CVC asked the court to review and reverse the PTAB's February 2017 decision, which terminated the interference without determining which inventors first invented the use of the CRISPR/Cas9 genome editing technology in eukaryotic cells. The Federal Circuit conducted a hearing on the appeal on April 30, 2018, and on September 10, 2018, affirmed the PTAB's decision to terminate the interference proceeding. As a result of the Federal Circuit's decision, U.S. Serial No. 13/842,859, which was previously considered allowable, was released from the interference and returned to the USPTO.

In parallel, either party can pursue and has pursued existing or new patent applications in the U.S. and elsewhere. Going forward, either party as well as other parties could seek a new interference related to the uses of the technology in eukaryotic cells or other aspects of the technology, and any existing or new patents could be the subject of other challenges to their validity of enforceability. In the context of a second interference or in other proceedings, a determination could be reached regarding that the Senior Party was not the first to invent, or it could be concluded that the contested subject matter is not patentable to the Senior Party and is patentable to the Junior Party, which in this case could preclude our U.S. patent applications from issuing as patents, in which case the proceedings would result in our losing the right to protect core innovations and our freedom to practice our core gene editing technology. If there is a second interference, either party can again appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In any case, it may be years before there is a final determination on priority. Pursuant to the terms of the license agreement with Dr. Charpentier, we are responsible for covering or reimbursing Dr. Charpentier's patent prosecution defense and related costs associated with our in-licensed technology. Furthermore, we may be involved in other interference proceedings or other disputes in the future.

In addition, Toolgen Inc. (Toolgen), filed Suggestions of Interference in the USPTO on April 13, 2015, and December 3, 2015, suggesting that it believes some of the claims pending in its applications (U.S. Serial No. 14/685,568 and U.S. Serial No. 14/685,510) interfere with certain claims in five of the Broad patents previously involved in the prior interference with CVC. The USPTO may, in the future, declare an interference between one or more of the patents and/or patent applications in the Patent Portfolio and one or more Toolgen patents and/or patent applications. We are also aware of additional third parties that have pending patent applications relating to CRISPR technologies, which similarly may or may not lead to further interference proceedings.

The patents and patent applications within the Patent Portfolio are subject to and may in the future become involved in similar proceedings or priority disputes in Europe or other foreign jurisdictions. For example, the Opposition Division has initiated opposition proceedings against European Patent Nos. EP 2,800,811 B1 and EP 3,241,902 B1. The EPO opposition proceedings may involve issues including, but not limited to, procedural formalities related to filing the European patent application, priority, and the patentability of the involved claims. We cannot be certain which of these results, if any, will actually occur or at what time, and the effects that any such results may have on us and our intellectual property position are currently unknown.

For example, Toolgen Inc., or Toolgen, filed Suggestions of Interference in the USPTO on April 13, 2015, and December 3, 2015, suggesting that they believe some of the claims in pending U.S. applications owned by Toolgen (U.S. Serial No. 14/685,568 and U.S. Serial No. 14/685,510, respectively) interfere with certain claims in five of the Broad patents previously involved in the interference with Dr. Charpentier, California and Vienna. The USPTO may, in the future, declare an interference between our patent application and one or more Toolgen, patent applications. We are also aware of additional third parties that have pending patent applications relating to CRISPR technologies, which similarly may or may not lead to further interference proceedings. For example Vilnius University has filed applications in the United States and in other jurisdictions (published internationally as WO2013/141680 and WO2013/142578 and granted as a patent in the United States as U.S. Patent No. 9,637,739), Harvard University has filed applications in the United States and in other jurisdictions (published internationally as WO2014/099744 and granted as a patent in the United States as U.S. Patent No. 9,023,649), and Sigma-Aldrich has filed applications in the United States and in other jurisdictions (published internationally as WO2014/089290), each claiming aspects of gene-editing technology based on applications claiming priority to provisional filings in 2012. Numerous other filings are based on provisional applications filed after 2012.

Broad, Toolgen, Vilnius, Harvard, Sigma-Aldrich and other parties routinely file international counterparts of their U.S. applications, some of which have been granted or could in future be granted in Europe and/or other non-U.S. jurisdictions. We and third parties have initiated opposition proceedings against some of these grants, and we may in the future oppose other grants to these or other applicants. For example, we and eight other entities have opposed European Patent 2771468 that was granted to Broad, MIT and Harvard. In hearings which began on January 16, 2018, the patent granted to Broad, MIT and Harvard was revoked, but the patentees have appealed the decision against them. Oppositions are also now pending with respect to a number of other patents granted to them in Europe. Similarly, our intellectual property may in the future become involved in opposition proceedings in Europe or other jurisdictions. For example, issued European patents we in-licensed from Dr. Charpentier have been opposed by multiple third parties. The oppositions to the European patents could lead to the revocation of the patents in whole or in part, or could lead to the claims being narrowed in a way that could impair or preclude our ability to enforce the patents against competitors in Europe.

Government Regulation

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

Licensure and Regulation of Biologics in the United States

In the United States, our product candidates are regulated as biological products, or biologics, under the Public Health Service Act, or PHSA, and the Federal Food, Drug, and Cosmetic Act, or FDCA, and their implementing regulations. The failure to comply with the applicable U.S. requirements at any time during the product development process, including nonclinical testing, clinical testing, the approval process or post-approval process, may subject an applicant to delays in the conduct of a study, regulatory review and approval, and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical testing, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, untitled or warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, and civil or criminal investigations and penalties brought by the FDA or the Department of Justice, or DOJ, or other governmental entities.

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

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated, or by a central IRB if appropriate;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency, and purity of the product candidate for each proposed indication, in accordance with the FDA's Good Clinical Practice, or GCP, regulations;
- preparation and submission to the FDA of a Biologics License Application, or BLA, for a biologic product requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product and proposed labeling;
- review of the product by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, at which the product, or components thereof, are produced to assess compliance with cGMP requirements and to assure that the facilities, methods, and controls are adequate to preserve the product's identity, strength, quality, and purity, and, if applicable, the FDA's current good tissue practice, or CGTP, for the use of human cellular and tissue products;
- satisfactory completion of any FDA audits of the nonclinical study and clinical trial sites to assure compliance with GLPs and GCPs, respectively, and the integrity of clinical data in support of the BLA;
- payment of user fees and securing FDA approval of the BLA; and

- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, adverse event reporting, and compliance with any post-approval studies required by the FDA.

Preclinical Studies and Investigational New Drug Application

Before testing any biologic product candidate in humans, including a gene therapy product candidate, the product candidate must undergo preclinical testing. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as studies to evaluate the potential for efficacy and toxicity in animals. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA imposes a clinical hold based on concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects would be exposed to unreasonable and significant health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin.

As a result, submission of the IND may result in the FDA not allowing the trials to commence or allowing the trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the conduct of the IND study, including safety concerns or concerns due to non-compliance, it may impose a partial or complete clinical hold. This order issued by the FDA would delay either a proposed clinical study or cause suspension of an ongoing study, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed or recommence but only under terms authorized by the FDA. This could cause significant delays or difficulties in completing planned clinical studies in a timely manner.

Human Clinical Trials in Support of a BLA

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

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a non-U.S. clinical trial is not conducted under an IND, the sponsor may submit data from a well-designed and well-conducted clinical trial to the FDA in support of the BLA so long as the clinical trial is conducted in compliance with GCP and the FDA is able to validate the data from the study through an onsite inspection if the FDA deems it necessary.

Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, subject informed consent, ethical factors, and the safety of human subjects. An IRB must operate in compliance with FDA regulations. The FDA or the clinical trial sponsor may suspend or terminate a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or the 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 drug has been associated with unexpected serious harm to patients. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group may recommend continuation of the study as planned, changes in study conduct, or cessation of the study at designated check points based on access to certain data from the study. Finally, research activities involving infectious agents, hazardous chemicals, recombinant DNA, and genetically altered organisms and agents may be subject to review and approval of an Institutional Biosafety Committee, or IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution established under the National Institutes of Health, or NIH, Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. The IBC assess the safety of the research and identifies any potential risk to public health or the environment.

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

- ***Phase 1*** clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion, and pharmacodynamics in healthy humans or, on occasion, in patients, such as cancer patients.
- ***Phase 2*** clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and costlier Phase 3 clinical trials.
- ***Phase 3*** clinical trials are undertaken within an expanded patient population to further evaluate dosage and gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.

Progress reports detailing the results, if known, of the clinical trials must be submitted at least annually to the FDA. Written IND safety reports must be submitted to the FDA and the investigators within 15 calendar days after determining that the information qualifies for reporting. IND safety reports are required for serious and unexpected suspected adverse events, findings from other studies or animal or *in vitro* testing that suggest a significant risk to humans exposed to the drug, and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Additionally, a sponsor must notify FDA within 7 calendar days after receiving information concerning any unexpected fatal or life-threatening suspected adverse reaction.

In some cases, the FDA may approve a BLA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of biologics approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Special Regulations and Guidance Governing Gene Therapy Products

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

Although the FDA has indicated that its guidance documents regarding gene therapies are not legally binding, we believe that our compliance with them is likely necessary to gain approval for any product candidate we may develop. The guidance documents provide additional factors that the FDA will consider at each of the above stages of development and relate to, among other things, the proper preclinical assessment of gene therapies; the chemistry, manufacturing, and control information that should be included in an IND application; the proper design of tests to measure product potency in support of an IND or BLA application; and measures to observe delayed adverse effects in subjects who have been exposed to investigational gene therapies when the risk of such effects is high. Further, the FDA usually recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by 10 years of annual queries, either in person or by questionnaire.

Previously, if a gene therapy trial was conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, a protocol and related documentation were required to be submitted to, and the study registered with, the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines prior to the submission of an IND to the FDA. In addition, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily followed them. The NIH would convene the Recombinant DNA Advisory Committee, or RAC, a federal advisory committee, to discuss protocols that raised novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA notified the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OBA web site and may be accessed by the public. In August 2018, the NIH published a notice in the Federal Register to seek public comment on its proposal to amend the NIH Guidelines to streamline oversight for human gene transfer clinical research protocols and reduce duplicative reporting requirements while focusing the NIH Guidelines more specifically on biosafety issues associated with research involving recombinant or synthetic nucleic acid molecules. The notice included proposed amendments to eliminate RAC

review and reporting requirements to NIH for human gene transfer research protocols and to modify the roles and responsibilities of investigators, institutions, IBCs, the RAC, and the NIH to be consistent with these goals. During the comment period and effective August 2018, the NIH stated it will no longer accept new human gene transfer protocols for the protocol registration process under the NIH Guidelines, or convene the RAC to review individual human gene transfer protocols. The NIH Office of Science Policy also will not accept annual reports, safety reports, amendments or other documentation for any previously registered human gene transfer protocols under the NIH Guidelines. The roles and responsibilities of IBCs at the local level will continue as described in the NIH Guidelines. Such trials remain subject to FDA and other clinical trial regulations, and only after FDA, IBC and other relevant approvals are in place can these protocols proceed. During this time, IBCs and IRBs will not be required to submit documentation to the NIH assessing whether a particular protocol meets the criteria for RAC review.

Compliance with cGMP and CGTP Requirements

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

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

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies for products intended for the U.S. market, and with analogous health regulatory agencies for products intended for other markets globally. Both U.S. and non-U.S. manufacturing establishments must register and provide additional information to the FDA and/or other health regulatory agencies upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether U.S. or non-U.S., is deemed misbranded under the FDCA, and could be affected by similar as well as additional compliance issues in other jurisdictions. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Manufacturers may also have to provide, on request, electronic or physical records regarding their establishments. Delaying, denying, limiting, or refusing inspection by the FDA or other governing health regulatory agency may lead to a product being deemed to be adulterated.

Review and Approval of a BLA

The results of product candidate development, preclinical testing, and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of a BLA requesting a license to market the product. The BLA must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee.

The FDA has 60 days after submission of the application to conduct an initial review to determine whether it is sufficient to accept for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or the PDUFA, the FDA has ten months in which to complete its initial review of a standard application and respond to the applicant, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs. The review process may often be significantly extended by FDA requests for additional information or clarification. The review process and the PDUFA goal date may be extended by three months if the FDA requests or if the applicant otherwise provides through the submission of a major amendment additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Under the PHSA, the FDA may approve a BLA if it determines that the product is safe, pure, and potent and the facility where the product will be manufactured meets standards designed to ensure that it continues to be safe, pure, and potent.

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of nonclinical study and clinical trial sites to assure compliance with GLPs and GCPs, respectively, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing

of the product with specific prescribing information for specific indications. If the application is not approved, the FDA will issue a complete response letter, which will contain the conditions that must be met in order to secure final approval of the application, and when possible will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a complete response letter may submit to the FDA information that represents a complete response to the issues identified by the FDA. Such resubmissions are classified under PDUFA as either Class 1 or Class 2. The classification of a resubmission is based on the information submitted by an applicant in response to an action letter. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has two months to review a Class 1 resubmission and six months to review a Class 2 resubmission. The FDA will not approve an application until issues identified in the complete response letter have been addressed. Alternatively, sponsors that receive a complete response letter may either withdraw the application or request a hearing.

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

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

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, and priority review designation.

Specifically, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process, or if the designated drug development program is no longer being pursued.

Second, FDA has a new regulatory scheme allowing for expedited review of products designated as "breakthrough therapies." A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting adverse reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and

evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

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

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally could support accelerated approval where a study demonstrates a relatively short-term clinical benefit in a chronic disease setting in which assessing durability of the clinical benefit is essential for traditional approval, but the short-term benefit is considered reasonably likely to predict long-term benefit.

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

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Post-Approval Regulation

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

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

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or

clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences of a failure to comply with regulatory requirements include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of licensed and approved products that are placed on the market. Pharmaceutical 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.

Orphan Drug Designation

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

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

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

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a second application for a clinically superior version of the product for the same use. The FDA cannot, however, approve the same product made by another manufacturer for the same indication during the market exclusivity period unless it has the consent of the sponsor or the sponsor is unable to provide sufficient quantities.

Pediatric Studies and Exclusivity

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

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, which was signed into law in March 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 or BPCIA. The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars.

Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity, and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

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

Patent Term Restoration and Extension

A patent claiming a new biologic product may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of an IND and the submission date of a marketing application, plus the time between the submission date of the marketing application and the ultimate approval date, less any time the applicant failed to act with due diligence. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Regulation And Procedures Governing Approval Of Medicinal Products In The European Union

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

Clinical Trial Approval

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

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new Clinical Trials Regulation (EU) No 536/2014 is expected to become applicable in 2019. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new legislation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single-entry point and strictly defined deadlines for the assessment of clinical trial applications.

Marketing Authorization

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

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all EU member states. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Specifically, the grant of marketing authorization in the European Union for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation (EC) No 1394/2007 on advanced therapy medicinal products, read in combination with Directive 2001/83/EC of the European Parliament and of the Council, commonly known as the Community code on medicinal products. Regulation (EC) No 1394/2007 lays down specific rules concerning the authorization, supervision, and pharmacovigilance of gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products. Manufacturers of advanced therapy medicinal products must demonstrate the quality, safety, and efficacy of their products to EMA which provides an opinion regarding the application for marketing authorization. The European Commission grants or refuses marketing authorization in light of the opinion delivered by EMA.

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

Regulatory Data Protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the

additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

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

Regulatory Requirements after Marketing Authorization

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

Orphan Drug Designation and Exclusivity

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

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

For other markets in which we might in future seek to obtain marketing approval for the commercialization of products, there are other health regulatory regimes for seeking approval, and we would need to ensure ongoing compliance with applicable health regulatory procedures and standards, as well as other governing laws and regulations for each applicable jurisdiction.

Coverage, Pricing and Reimbursement

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

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

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

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

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

country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare Law and Regulation

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

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil U.S. False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious, or fraudulent or knowingly making, using, or causing to be made or used a false record or statement to avoid, decrease, or conceal an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the U.S. False Claims Act;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, (collectively "HIPAA") which imposes criminal and civil liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program (including private payors) 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;
- HIPAA, which impose obligations with respect to safeguarding the privacy, security, and transmission of individually identifiable information that constitutes protected health information, including mandatory contractual terms and restrictions on the use and/or disclosure of such information without proper authorization;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the U.S. Patient Protection and Affordable Care Act, as amended by the U.S. Health Care and Education Reconciliation Act, collectively the Affordable Care Act or ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, and requires certain manufacturers and applicable group purchasing organizations to report ownership and investment interests held by physicians or their immediate family members;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- The Foreign Corrupt Practices Act, or FCPA, prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment; and
- analogous laws and regulations in other national jurisdictions and states, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

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

Healthcare Reform

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

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for products that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable products to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient products to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription product spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, 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 2012 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 up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several

providers, including hospitals, imaging centers, and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Since its enactment, some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial, Congressional, and Executive challenges. In 2012, the U.S. Supreme Court upheld certain key aspects of the legislation, including a tax-based shared responsibility payment imposed on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly the requirement that all individuals maintain health insurance coverage or pay a penalty, referred to as the "individual mandate." Though Congress has not passed repeal legislation to date, the 2017 Tax Reform Act included a provision which repealed the individual mandate effective January 1, 2019. On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. It is unclear how this decision and any subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business.

On January 20, 2017, United States President Donald Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the Affordable Care Act to waive, defer, grant exemptions from, or delay the implementation of any provision of the Affordable Care Act that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. A second Executive Order signed in 2017 terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the cost share reduction payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Congress continues to consider subsequent legislation to replace elements of the Affordable Care Act or to repeal it entirely. It is unclear whether new legislation modifying the Affordable Care Act will be enacted, and, if so, precisely what the new legislation will provide, when it will be enacted and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare. We plan to continue to evaluate the effect that the Affordable Care Act and its possible repeal and replacement may have on our business.

Further, the Centers for Medicare & Medicaid Services, or CMS, recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. On November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule changes would allow Medicare Advantage plans to use pre authorization (PA) and step therapy (ST) for six protected classes of drugs, with certain exceptions, permit plans to implement PA and ST in Medicare Part B drugs; and change the definition of "negotiated prices" while a definition of "price concession" in the regulations. It is unclear whether these proposed changes we be accepted, and if so, what effect such changes will have on our business.

There has also been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. Individual states in the United States have also become increasingly active in enacting legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Beyond challenges to the ACA, other legislative measures have also been enacted that may impose additional pricing and product development pressures on our business. For example, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy. We expect that additional foreign, federal and state healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

There have been, and likely will continue to be, legislative and regulatory proposals at the national level in the U.S. and other jurisdictions globally, as well as at some regional, state and/or local levels within the U.S. or other jurisdictions, directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on

anticipated revenues from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

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 Conservation and Recovery Act, and the Toxic Substances Control Act, affect our business. These and other laws govern the use, handling, and disposal of various biologic, chemical, and radioactive substances used in, and wastes generated by, 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. Equivalent laws have been adopted in third countries that impose similar obligations.

Employees

As of December 31, 2018 we had 188 full-time employees, 56 of whom held Ph.D. or M.D. degrees, 153 of whom were engaged in research and development, and 35 of whom were engaged in business development, finance, information systems, facilities, human resources, legal functions, or administrative support. None of our employees is represented by a labor union, and none of our employees has entered into a collective bargaining agreement with us. We consider our employee relations to be good.

Information Available on the Internet

Investors and others should note that we announce material information to our investors using our investor relations website (https://crisprtx.gcs-web.com/), SEC filings, press releases, public conference calls and webcasts. We use these channels as well as social media to communicate with the public about our company, our business, our product candidates and other matters. It is possible that the information we post on social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the social media channels listed on our investor relations website.

Item 1A. Risk Factors.

This report contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those discussed in this report. Factors that could cause or contribute to these differences include, but are not limited to, those discussed below and elsewhere in this report and in any documents incorporated in this report by reference.

You should carefully consider the following risk factors, together with all other information in this report, including our financial statements and notes thereto, and in our other filings with the Securities and Exchange Commission. If any of the following risks, or other risks not presently known to us or that we currently believe to not be significant, develop into actual events, then our business, financial condition, results of operations or prospects could be materially adversely affected. If that happens, the market price of our common shares could decline, and shareholders may lose all or part of their investment.

Risks Related to Our Financial Position and Need for Additional Capital

We Have Incurred Significant Operating Losses Since Our Inception And Anticipate That We Will Incur Continued Losses For The Foreseeable Future.

We have funded our operations through public and private offerings of our equity securities, private placements of our preferred shares, convertible loans and collaboration agreements with strategic partners. Since inception, we have incurred significant operating losses. Our net loss was $165.0 million, $68.4 million and $23.2 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, and 2017, we had an accumulated deficit of $291.6 million and $125.4 million, respectively. We expect to continue to incur significant expenses and operating losses over the next several years and for the foreseeable future. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' deficit and working capital. We anticipate that our expenses will increase substantially if and as we:

- continue our clinical trials for our lead hemoglobinopathy program, CTX001, targeting beta thalassemia and sickle cell disease
- continue our current research programs and our preclinical and clinical development of product candidates;
- seek to identify additional research programs and additional product candidates;
- conduct Investigational New Drug, or IND, supporting preclinical studies and initiate clinical trials for our most advanced product candidates which are from our hemoglobinopathy program targeting beta thalassemia and sickle cell disease;
- initiate preclinical studies and clinical trials for any other product candidates we identify and choose to develop;
- expand, maintain, enforce and/or defend our intellectual property estate;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- further develop our gene editing technology;
- hire additional clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product candidate development;
- acquire or in-license other technologies;
- ultimately establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval; and
- operate as a public company.

As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing gene editing product candidates, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

We Will Need To Raise Substantial Additional Funding, Which Will Dilute Our Shareholders. If We Are Unable To Raise Capital When Needed, We Would Be Forced To Delay, Reduce Or Eliminate Some Of Our Product Development Programs Or Commercialization Efforts.

The development of gene editing product candidates is capital intensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate preclinical studies and clinical trials for and seek marketing approval for our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that such sales, marketing, manufacturing and distribution are not the responsibility of Bayer Healthcare or Vertex, or other future collaborators. We may also need to raise additional funds sooner if we choose to pursue additional indications or geographies for our product candidates or otherwise expand more rapidly than we presently anticipate. In addition, relative to prior years when we were a private company, we expect to incur significant additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate certain of our research and development programs or future commercialization efforts.

As of December 31, 2018, and 2017, we had cash of approximately $456.6 million and $239.8 million, respectively. In January 2018, the Company completed an offering of 5,750,000 shares of common, which were sold at a price of $22.75 per share. This offering resulted in net proceeds of $122.6 million. In August 2018, we entered into an At-The-Market ("ATM") sales agreement with Jefferies LLC ("Jefferies"), under which we may offer and sell from time to time common shares having aggregate gross proceeds of up to $125.0 million. We have not yet issued or sold any securities under this sales agreement. In September 2018, we completed an offering of 4,210,526 common shares, which were sold at a price to the public of $47.50 per share. This offering resulted in net proceeds of $187.6 million. With our cash on hand as of December 31, 2018, we expect cash and cash equivalents to be sufficient to fund its current operating plan through at least the next 24 months.

Our future capital requirements will depend on, and could increase significantly as a result of, many factors, including:

- the scope, progress, results and costs of clinical trials, drug discovery, preclinical development, and laboratory testing for our wholly owned and partnered product candidates;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of establishing and maintaining a supply chain for the development and manufacture of our product candidates;
- the success of our current joint venture with Bayer Healthcare and our collaboration with Vertex;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any additional collaboration agreements we obtain;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs of fulfilling our obligations under the Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement to reimburse other parties for costs incurred in connection with the prosecution and maintenance of associated patent rights;
- the extent to which we acquire or in-license other product candidates and technologies;
- the costs of establishing or contracting for manufacturing capabilities if we obtain regulatory approvals to manufacture our product candidates;
- the costs of establishing or contracting for sales and marketing capabilities if we obtain regulatory approvals to market our product candidates; and
- our ability to establish and maintain healthcare coverage and adequate reimbursement.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. We cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our shareholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our shareholders and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. The

incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborators or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

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

We Have A Limited Operating History, Which May Make It Difficult To Evaluate Our Technology And Product Development Capabilities And Predict Our Future Performance.

We were formed in October 2013, have no products approved for commercial sale and have not generated any revenue from product sales. Our ability to generate product revenue or profits, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. We may never be able to develop or commercialize a marketable product.

We are early in our development efforts and the first clinical trial for any of our product candidates was initiated at the end of 2018. Each of our other programs requires additional discovery research and then preclinical development. All of our programs, including our hemoglobinopathy program, require 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 health regulatory agencies, including the European Medicines Agency, or EMA, before we may commercialize any product.

Our limited operating history, particularly in light of the rapidly evolving gene editing field, may make it difficult to evaluate our technology and industry and predict our future performance. Our short history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early stage companies in rapidly evolving fields. If we do not address these risks successfully, our business will suffer. Similarly, we expect that our financial condition and operating results will fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. As a result, our shareholders should not rely upon the results of any quarterly or annual period as an indicator of future operating performance.

In addition, as an early stage company, we have encountered unforeseen expenses, difficulties, complications, delays and other known and unknown circumstances. As we advance our product candidates, we will need to transition from a company with a research focus to a company capable of supporting clinical development and if successful, commercial activities. We may not be successful in such a transition.

Our Ability To Use Tax Loss Carryforwards In Switzerland May Be Limited.

Under Swiss law, we are entitled to carry forward losses we incur for a period of seven years and we can offset future profits, if any, against such losses. As of December 31, 2017, we reported tax loss carry forwards from inception through 2017 for purposes of Swiss federal direct taxes in the aggregate amount of CHF 103 million. As we moved our legal seat from the Canton of Basel-Stadt to the Canton of Zug mid of 2017, it will be the Canton of Zug, which is in charge for assessing our tax return including our carry forward losses. No ruling regarding taxation as a mixed company has been filed with the Zug tax authorities; however, based on the practice of the Canton of Zug, we can apply for the taxation as mixed company in the tax return as long as the respective law is in force and we fulfill the respective criteria. According to the practice of the Canton of Zug the tax loss carry forwards at cantonal level are the same as at federal level. Therefore, in aggregate as of December 31, 2017 tax loss carry forwards of CHF 103 million have been reported at cantonal level as well. At January 1, 2018, for the purposes of our Swiss statutory financial statements, we changed our functional currency from CHF to USD. Because Swiss tax laws align with Swiss statutory financial reporting, this resulted in a remeasurement of our Swiss net operating loss carry forwards as of January 1, 2018. According to statutory Swiss accounting law, the translation has to take place at the closing rate as per December 31, 2017. For this purpose, we applied the spot rate of CHF/USD of 1.02438. Although there is no explicit regulation in the law or guideline published by the tax authorities, as the conversion at the closing rate is in accordance with statutory accounting law, it is also to be considered applicable for corporate income tax purposes. Therefore, the tax loss carry forwards as per January 1, 2018 amount to USD 106 million and the tax loss carry forwards as per December 31, 2018 amount to USD 270 million (including the loss 2018 of USD 164 million). It is to be noted in this regard that tax

losses are only finally assessed by the tax authorities when offset with taxable profit (which will not be the case as long we are loss making). If not used, these tax losses will expire seven years after the year in which they occurred. Due to our limited income, there is a high risk that the tax loss carry forwards will expire partly or entirely and as a result they would not be applied to reduce future cash tax payments. These carry forwards are fully reserved and will remain so until we become consistently profitable. For 2018, the tax return has – in accordance with Swiss tax law – not yet been filed. Therefore, for 2018 the loss carried forward will only be claimed with filing of the tax return for the tax year 2018.

The statutory corporate profit tax rate in the Canton of Zug amounts to 16.98% (federal, cantonal and communal) of the profit after taxes (taxes are deductible). As already mentioned above, no tax ruling was filed with the Zug tax authorities for applying for the taxation as mixed company. However, as long as the respective law is in force and we fulfill the criteria, a respective application for taxation as a mixed company can be made in the annual tax return and will be granted by the Zug tax authorities. The statutory corporate profit tax rate (on the profit after tax) as mixed company in the Canton of Zug ranges between 9.35% and 10.62% on the profit after taxes (taxes are deductible), depending on the number of full-time equivalents employed in Switzerland in a given year. The maximum tax rate applies in case we employ more than 30 full time equivalents by the end of a given year. The Canton does from time to time amend the level of taxation levied on corporations and there is no certainty that the tax rate currently in effect will not change in the future.

The privileges for mixed companies are under pressure and new tax legislations abolish mixed companies but at the same time lowering the ordinary tax rate is in preparation (e.g. the Canton of Zug has announced a planned reduction of its effective income tax rate to 12-12.5% (federal and cantonal)). In May 2019 a public vote on the new tax legislations takes place at Federal level. If accepted, the new legislation may potentially come into force in 2020, whereby changes in the cantonal law may be subject to confirmation by a public vote as well. This cantonal vote may cause a delay on the implementation of lower tax rates at cantonal level.

Risks Related to Our Business, Technology and Industry

We Are Early In Our Development Efforts. It Will Be Many Years Before We Or Our Collaborators Commercialize A Product Candidate, If Ever. If We Are Unable To Advance Our Product Candidates To Clinical Development, Obtain Regulatory Approval And Ultimately Commercialize Our Product Candidates, Or Experience Significant Delays In Doing So, Our Business Will Be Materially Harmed.

We are early in our development efforts and have focused our research and development efforts to date on CRISPR/Cas9, gene editing technology, identifying our initial targeted disease indications and our initial product candidates. Our future success depends heavily on the successful development of our CRISPR/Cas9 gene editing product candidates including our most advanced product candidate, CTX001, which targets beta thalassemia and sickle cell disease. We have invested substantially all of our efforts and financial resources in the identification and preclinical development of our current product candidates. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. For example, our research programs, including those subject to our joint venture with Bayer Healthcare and Collaboration Agreement and the Joint Development and Commercialization Agreement, or the JDA, with Vertex, may fail to identify potential product candidates for clinical development for a number of reasons or may fail to successfully advance any product candidates through clinical development. Our research methodology may be unsuccessful in identifying potential product candidates, or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products impractical to manufacture, unmarketable, or unlikely to receive marketing approval. We currently generate no revenue from sales of any product and we may never be able to develop or commercialize a marketable product.

Since December 2017, we have submitted CTAs in various European jurisdictions and Canada for CTX001 to begin our first clinical trial in beta thalassemia, and we have submitted CTAs in various European jurisdictions and Canada and filed an IND with the FDA to begin our first clinical trial for CTX001 in sickle cell disease. The filing of future CTAs or INDs for any other product candidate we develop is subject to the identification and selection of guide RNA with acceptable efficiency. Commencing any of our clinical trials is also subject to acceptance by the European regulatory authorities of our CTAs, or the FDA of our INDs, and finalizing the trial design based on discussions with the applicable regulatory authorities. In the event that the European regulatory authorities or FDA requires us to complete additional preclinical studies or we are required to satisfy other requests, our clinical trials may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, they could disagree that we have satisfied their requirements to commence our clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials or impose stricter approval conditions than we currently expect. Our product candidates will require additional preclinical and clinical development, regulatory and marketing 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 development programs must be approved for marketing by the FDA, EMA or certain other health regulatory agencies, before we may commercialize our product candidates.

The success of our product candidates will depend on several factors, including the following:

- successful completion of clinical trials and preclinical studies;
- sufficiency of our financial and other resources to complete the necessary clinical trials and preclinical studies;
- ability to develop safe and effective delivery mechanisms for our *in vivo* therapeutic programs;
- ability to identify optimal RNA sequences to guide genomic editing;
- entry into collaborations to further the development of our product candidates;
- approval of CTAs or INDs for our product candidates to commence clinical trials;
- successful enrollment in, and completion of, clinical trials and preclinical studies;
- successful data from our clinical program that supports an acceptable risk-benefit profile of our product candidates for the intended patient populations;
- receipt of regulatory and marketing approvals from applicable regulatory authorities;
- establishment of arrangements with third-party manufacturers for clinical supply and commercial manufacturing and, where applicable, commercial manufacturing capabilities;
- successful development of our internal manufacturing processes and transfer to larger-scale facilities operated by either a contract manufacturing organization, or CMO, or by us;
- establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates;
- commercial launch of our product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the product candidates, if and when approved, by patients, the medical community and third-party payors;
- effective competition with other therapies and treatment options;
- establishment and maintenance of healthcare coverage and adequate reimbursement;
- enforcement and defense of intellectual property rights and claims;
- maintenance of a continued acceptable safety profile of the product candidates following approval; and
- achieving desirable medicinal properties for the intended indications.

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

- regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future; to date, no products that involve the genetic modification of patient cells have been approved in the United States and only one gene therapy product has been approved in the European Union;
- improper insertion of a gene sequence into a patient's chromosome could lead to lymphoma, leukemia or other cancers, or other aberrantly functioning cells; and
- the FDA recommends a follow-up observation period of 15 years or longer for all patients who receive treatment using gene therapies, and we may need to adopt and support such an observation period for our product candidates.

If we do not succeed in one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business. If we do not receive regulatory approvals for our product candidates, we may not be able to continue our operations.

Our CRISPR/Cas9 Gene Editing Product Candidates Are Based On A New Gene Editing Technology, Which Makes It Difficult To Predict The Time And Cost Of Development And Of Subsequently Obtaining Regulatory Approval, If At All. There Have Only Been A Limited Number Of Clinical Trials Of Product Candidates Based On Gene Editing Technology And No Gene Editing Products Have Been Approved In The United States Or In The European Union.

CRISPR/Cas9 gene editing technology is relatively new, and no products based on CRISPR/Cas9 or other similar gene editing technologies have been approved in the United States or the European Union and only a limited number of clinical trials of products based on gene editing technologies have been commenced. As such it is difficult to accurately predict the developmental challenges we may incur for our product candidates as they proceed through product discovery or identification, preclinical studies and clinical trials. In addition, because we have only recently commenced clinical trials in CTX001, we have not yet been able to assess safety in humans, and there may be long-term effects from treatment with any product candidates that we develop that we cannot predict at this time. Any product candidates we may develop will act at the level of DNA, and, because animal DNA differs from human DNA, testing of our product candidates in animal models may not be predictive of the results we observe in human clinical trials of our product candidates for either safety or efficacy. Also, animal models may not exist for some of the diseases we choose to pursue in our programs. As a result of these factors, it is more difficult for us to predict the time and cost of product candidate development, and we cannot predict whether the application of our gene editing technology, or any similar or competitive gene editing technologies, will result in the identification, development, and regulatory approval of any products. There can be no assurance that any development problems we experience in the future related to our gene editing technology or any of our research programs will not cause significant delays or unanticipated costs, or that such development problems can be solved. Any of these factors may prevent us from completing our preclinical studies or any clinical trials that we may initiate or commercializing any product candidates we may develop on a timely or profitable basis, if at all.

The clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. No products based on gene editing technologies have been approved by regulators. As a result, the regulatory approval process for product candidates such as ours is uncertain and may be more expensive and take longer than the approval process for product candidates based on other, better known or more extensively studied technologies. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union or how long it will take to commercialize our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product candidate to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects may be harmed.

The FDA, The NIH And The EMA Have Demonstrated Caution In Their Regulation Of Gene Therapy Treatments, And Ethical And Legal Concerns About Gene Therapy And Genetic Testing May Result In Additional Regulations Or Restrictions On The Development And Commercialization Of Our Product Candidates, Which May Be Difficult To Predict.

The FDA, NIH and the EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. Within the broader genome product field, uniQure's Glybera® (Alipogene tiparvovec) has received marketing authorization from the European Commission.

Regulatory requirements in the United States and in other jurisdictions governing gene therapy products have changed frequently and may continue to change in the future. The FDA established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research to consolidate the review of gene therapy and related products, and established the Cellular, Tissue and Gene Therapies Advisory Committee to advise this review. In addition to the government regulators, the IBC and institutional review board, or IRB, of each institution at which we conduct clinical trials of our product candidates, or a central IRB if appropriate, would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, the EMA governs the development of gene therapies in the European Union and may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines. These regulatory review agencies and committees and the new requirements or guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies or trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory agencies and committees and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of such product candidates. These additional processes may result in a review

and approval process that is longer than we otherwise would have expected. Delays as a result of an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our or our collaborators' ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all.

If Any Of The Product Candidates We May Develop Or The Delivery Modes We Rely On Cause Undesirable Side Effects, It Could Delay Or Prevent Their Regulatory Approval, Limit The Commercial Potential Or Result In Significant Negative Consequences Following Any Potential Marketing Approval.

Product candidates we may develop may be associated with undesirable side effects, unexpected characteristics or other serious adverse events, including off-target cuts of DNA, or the introduction of cuts in DNA at locations other than the target sequence. These off-target cuts could lead to disruption of a gene or a genetic regulatory sequence at an unintended site in the DNA, or, in those instances where we also provide a segment of DNA to serve as a repair template, it is possible that following off-target cut events, DNA from such repair template could be integrated into the genome at an unintended site, potentially disrupting another important gene or genomic element. There also is the potential risk of delayed adverse events following exposure to gene editing therapy due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material. Possible adverse side effects that could occur with treatment with gene editing products include an immunologic reaction after administration which could substantially limit the effectiveness of the treatment. Additionally, immunotherapy, and its method of action of harnessing the body's immune system, is powerful and could lead to serious side effects that we only discover in clinical trials. Unforeseen side effects could arise either during clinical development or, if such side effects are more rare, after our product candidates have been approved by regulatory authorities and the approved product has been marketed, resulting in the exposure of additional patients. If our CRISPR/Cas9 gene editing technology demonstrates a similar effect, we may decide or be required to halt or delay preclinical development or clinical development of our product candidates. In addition to serious adverse events or side effects caused by any product candidate we may develop; the administration process or related procedures also can cause undesirable side effects. If any such events occur, our clinical trials could be suspended or terminated.

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

Additionally, if we successfully develop a product candidate and it receives marketing approval, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, to ensure that the benefits of treatment with such product candidate outweighs the risks for each potential patient, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, extensive patient monitoring, or distribution systems and processes that are highly controlled, restrictive, and more costly than what is typical for the industry. Furthermore, if we or others later identify undesirable side effects caused by any product candidate that we to develop, several potentially significant negative consequences could result, including:

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

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

If We Experience Delays Or Difficulties In The Enrollment Of Patients In Clinical Trials, Our Receipt Of Necessary Regulatory Approvals Could Be Delayed Or Prevented.

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

Patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- availability and efficacy of approved medications for the disease under investigation;
- availability of genetic testing for potential patients;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;
- eligibility and exclusion criteria for the trial in question;
- perceived risks and benefits of the product candidate under trial;
- perceived risks and benefits of gene editing and cellular therapies as therapeutic approaches;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

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

Positive Results From Early Preclinical Studies Of Our Product Candidates Are Not Necessarily Predictive Of The Results Of Later Preclinical Studies And Any Future Clinical Trials Of Our Product Candidates. If We Cannot Replicate The Positive Results From Our Earlier Preclinical Studies Of Our Product Candidates In Our Later Preclinical Studies And Future Clinical Trials, We May Be Unable To Successfully Develop, Obtain Regulatory Approval For And Commercialize Our Product Candidates.

Any positive results from our preclinical studies of our product candidates may not necessarily be predictive of the results from required later preclinical studies and clinical trials. Similarly, even if we are able to complete our planned preclinical studies or any future clinical trials of our product candidates according to our current development timeline, the positive results from such preclinical studies and clinical trials of our product candidates may not be replicated in subsequent preclinical studies or clinical trial results.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials 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 and other nonclinical findings made while clinical trials were underway or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events. Moreover, preclinical, nonclinical and clinical data are often susceptible to varying interpretations and analyses and many companies

that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval.

Even If We Complete The Necessary Preclinical Studies And Clinical Trials, The Marketing Approval Process Is Expensive, Time-Consuming, And Uncertain And May Prevent Us From Obtaining Approvals For The Commercialization Of Any Product Candidates We May Develop. If We Are Not Able To Obtain, Or If There Are Delays In Obtaining, Required Regulatory Approvals, We Will Not Be Able To Commercialize, Or Will Be Delayed In Commercializing, Product Candidates We May Develop, And Our Ability To Generate Revenue Will Be Materially Impaired.

Any product candidates we may develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale, and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States, by EMA in the European Union and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval or clearance to market any product candidates from regulatory authorities in any jurisdiction and it is possible that none of our product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval or clearance. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations, or CROs, or regulatory consultants to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity, efficacy and potency. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any product candidates we develop may not be effective, may be only moderately effective, or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

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

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

We May Never Obtain FDA Approval For Any Of Our Product Candidates In The United States, And Even If We Do, We May Never Obtain Approval For Or Commercialize Any Of Our Product Candidates In Any Other Jurisdiction, Which Would Limit Our Ability To Realize Their Full Market Potential.

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

Gene Editing Products Are Novel And May Be Complex And Difficult To Manufacture. We Could Experience Manufacturing Problems That Result In Delays In The Development Or Commercialization Of Our Product Candidates Or Otherwise Harm Our Business.

The manufacturing process used to produce CRISPR/Cas9-based product candidates may be complex, as they are novel and have not been validated for clinical and commercial production. Several factors could cause production interruptions, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers.

Our product candidates 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 biologics generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner. Accordingly, we will employ multiple steps to control the manufacturing process to assure 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 or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical grade materials that meet FDA, the EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, the FDA, the EMA and other health 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 health 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 or product recalls. Lot failures or product recalls 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.

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

Adverse Public Perception Of Gene Editing And Cellular Therapy Products May Negatively Impact Demand For, Or Regulatory Approval Of, Our Product Candidates.

Our product candidates involve editing the human genome. The clinical and commercial success of our product candidates will depend in part on public acceptance of the use of gene editing therapies for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene editing is unsafe, unethical, or immoral, and, consequently, our products may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy in general could result in greater government regulation and stricter labeling requirements of gene editing products, including any of our product candidates, and could cause a decrease in the demand for any products we may develop. Adverse public attitudes may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar and for which greater clinical data may be available.

In particular, gene editing technology is subject to public debate and heightened regulatory scrutiny due to ethical concerns relating to the application of gene editing technology to human embryos or the human germline. For example, in April 2016, Chinese scientists reported on their attempts to edit the genome of human embryos to modify the gene for hemoglobin beta. This is the gene in which a mutation occurs in patients with the inherited blood disorder beta thalassemia. Although this research was purposefully conducted in embryos that were not viable, the work prompted calls for a moratorium or other types of restrictions on gene editing of human eggs, sperm, and embryos. The Alliance for Regenerative Medicine in Washington, D.C. has called for a voluntary moratorium on the use of gene editing technologies, including CRISPR/Cas9, in research that involves altering human embryos or human germline cells. Similarly, the NIH has announced that it would not fund any use of gene editing technologies in human embryos, noting that there are multiple existing legislative and regulatory prohibitions against such work, including the Dickey-Wicker Amendment, which prohibits the use of appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. Laws in the United Kingdom prohibit genetically modified embryos from being implanted into women, but embryos can be altered in research labs under license from the Human Fertilisation and Embryology Authority. Research on embryos is more tightly controlled in many other European countries.

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

If, In The Future, We Are Unable To Establish Sales And Marketing Capabilities Or Enter Into Agreements With Third Parties To Sell And Market Products Based On Our Technologies, We May Not Be Successful In Commercializing Our Products If And When Any Products Candidates Are Approved And We May Not Be Able To Generate Any Revenue.

We do not currently have a sales or marketing 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 any 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 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; and
- unforeseen costs and expenses associated with creating an independent 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 and marketing 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.

Even If We, Or Any Collaborators We May Have, Obtain Marketing Approvals For Any Product Candidates We Develop, The Terms Of Approvals And Ongoing Regulation Of Our Products Could Require The Substantial Expenditure Of Resources And May Limit How We, Or They, Manufacture And Market Our Products, Which Could Materially Impair Our Ability To Generate Revenue.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising, and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, current Good Manufacturing Practice, or cGMP, requirements relating to quality control, quality assurance and corresponding maintenance of records and documents and requirements regarding recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. The FDA also may place other conditions on approvals including the requirement for a REMS to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the Biologics License

Application, or BLA, must submit a proposed REMS before it can obtain approval. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

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

Any Product Candidate For Which We Obtain Marketing Approval Could Be Subject To Restrictions Or Withdrawal From The Market, And We May Be Subject To Substantial Penalties If We Fail To Comply With Regulatory Requirements Or If We Experience Unanticipated Problems With Our Products, When And If Any Of Them Are Approved.

The FDA and other regulatory agencies closely regulate the post-approval marketing and promotion of biologics to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and other regulatory agencies impose stringent restrictions on manufacturers' communications regarding off-label use, and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing by the FDA and other federal and state enforcement agencies, including the United States Department of Justice. Violation of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription products may also lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws.

In addition, later discovery of previously unknown problems with a product candidate, including adverse events of unanticipated severity or frequency, or with our manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

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

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

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

commercialize any product candidates we may develop and adversely affect our business, financial condition, results of operations, and prospects.

The Commercial Success Of Any Of Our Product Candidates Will Depend Upon Its Degree Of Market Acceptance By Physicians, Patients, Third-party Payors And Others In The Medical Community.

Ethical, social and legal concerns about gene therapy could result in additional regulations restricting or prohibiting our products. Even with the requisite approvals from FDA in the United States, the EMA in the European Union and other regulatory authorities internationally, the commercial success of our product candidates will depend, in significant part, on the acceptance of physicians, patients and health care payors of gene therapy products in general, and our product candidates in particular, as medically necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and others in the medical community. The degree of market acceptance of gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including:

- the efficacy, durability and safety of such product candidates as demonstrated in any future clinical trials;
- the potential and perceived advantages of product candidates over alternative treatments;
- the cost of treatment relative to alternative treatments;
- the clinical indications for which the product candidate is approved by FDA or the EMA
- patient awareness of, and willingness to seek, genotyping;
- the willingness of physicians to prescribe new therapies;
- the willingness of the target patient population to try new therapies;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of FDA, the EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party payor coverage and reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and future clinical trials, market acceptance of the product will not be fully known until after it is launched. If our product candidates do not achieve an adequate level of acceptance following regulatory approval, if ever, we may not generate significant product revenue and may not become profitable.

We May Expend Our Limited Resources To Pursue A Particular Product Candidate Or Indication And Fail To Capitalize On Product Candidates Or Indications That May Be More Profitable Or For Which There Is A Greater Likelihood Of Success.

We have limited financial and managerial resources. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to timely capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We Face Significant Competition In An Environment Of Rapid Technological Change And The Possibility That Our Competitors May Achieve Regulatory Approval Before Us Or Develop Therapies That Are More Advanced Or Effective Than Ours, Which May Harm Our Business And Financial Condition, And Our Ability To Successfully Market Or Commercialize Our Product Candidates.

The biotechnology and pharmaceutical industries, including in the gene therapy and gene editing fields, are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on intellectual property and proprietary products. 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, some or all of which may have greater access to capital or resources than we do.

We are aware of several companies focused on developing gene editing in various indications using CRISPR/Cas9 gene editing technology, including Intellia Therapeutics, Inc. and Editas Medicine, Inc., or Editas. There can be no certainty that other gene editing technologies will not be considered better or more attractive than our technology for the development of products. For example, Editas has exclusively licensed a CRISPR system involving a different protein, Cpf1, which can also edit human DNA as well as advanced forms of Cas9. Editas and certain of its scientific founders have asserted that Cpf1 may work better than Cas9 in some cases. Cas9 may be determined to be less attractive than Cpf1 or other CRISPR proteins that have yet to be discovered.

There are additional companies developing therapies using additional gene editing technologies, including transcription activator-like effector nucleases (TALENs), meganucleases and zinc finger nucleases (ZFNs). These companies include Allogene Therapeutics, bluebird bio, Cellectis, Precision BioSciences, and Sangamo Therapeutics.

We are also aware that other companies are developing gene and cell therapy products more generally, including Abeona Therapeutics, Adverum Biotechnologies, Celgene, Fate Therapeutics, Gilead Sciences, Novartis Pharmaceuticals, Orchard Therapeutics, Poseida Therapeutics, REGENXBIO, and Sarepta Therapeutics.

In addition to competition from other gene editing therapies or gene therapies, any product we may develop may also face competition from other types of therapies, such as small molecule, antibody or protein therapies. In addition, new scientific discoveries may cause CRISPR/Cas9 technology, or gene editing as a whole, to be considered an inferior form of therapy.

Many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, have broader acceptance and higher rates of reimbursement by third party payors or are less expensive than any products that we may develop or that would render any products that we may develop obsolete or non-competitive. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products and our patents may not be sufficient to prevent our competitors from commercializing competing products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

To become and remain profitable, we must develop and eventually commercialize product candidates with significant market potential, which will require us to be successful in a range of challenging activities. These activities can include completing preclinical studies and clinical trials of our product candidates, obtaining marketing and reimbursement approval for these product candidates, manufacturing, marketing and selling those products that are approved and satisfying any post marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our Company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our Company also could cause shareholders to lose all or part of their investment.

Even If We Are Able To Commercialize Any Product Candidates, Such Products May Become Subject To Unfavorable Pricing Regulations, Third-party Reimbursement Practices, Or Healthcare Reform Initiatives, Which Would Harm Our Business.

The regulations that govern marketing approvals, pricing, and reimbursement for new biologic products vary widely from country to country. Some countries require approval of the sale price of a product before it can be marketed. In many countries, the

pricing review period begins after marketing or product licensing approval is granted. In some non-U.S. markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval.

Our ability to commercialize any products successfully also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product that we commercialize and, if reimbursement is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval.

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

Risks Related to Our Relationships with Third Parties

If Conflicts Arise Between Us And Our Collaborators Or Strategic Partners, These Parties May Act In A Manner Adverse To Us And Could Limit Our Ability To Implement Our Strategies.

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

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

Our Collaborators Or Strategic Partners May Decide To Adopt Alternative Technologies Or May Be Unable To Develop Commercially Viable Products With Our Technology, Which Would Negatively Impact Our Revenues And Our Strategy To Develop These Products.

Our collaborators or strategic partners may adopt alternative technologies, which could decrease the marketability of our CRISPR/Cas9 gene editing technology. Additionally, because our current collaborators or strategic partners are and we anticipate that any future collaborators or strategic partners will be working on more than one development project, they could choose to shift their resources to projects other than those they are working on with us. If they do so, this would delay our ability to test our technology and would delay or terminate the development of potential products based on our CRISPR/Cas9 gene editing technology. Further, our

collaborators and strategic partners may elect not to develop products arising out of our collaborative and strategic partnering arrangements or to devote sufficient resources to the development, manufacturing, marketing or sale of these products. The failure to develop and commercialize a product candidate pursuant to our agreements with our current or future collaborators would prevent us from receiving future milestone and royalty payments which would negatively impact our revenues.

Our Collaborators And Strategic Partners May Control Aspects Of Our Clinical Trials and Commercialization Efforts, Which Could Result In Delays And Other Obstacles In The Commercialization Of Our Proposed Products And Materially Harm Our Results Of Operations.

For some programs, we will depend on third party collaborators and strategic partners to design and conduct our clinical trials, and for any approved products, the commercialization of such products. As a result, we may not be able to conduct these programs in the manner or on the time schedule we currently contemplate, which may negatively impact our business operations. In addition, if any of these collaborators or strategic partners withdraw support for our programs or proposed products or otherwise impair their development or commercialization, our business could be negatively affected. In October 2015, we entered into a four-year collaboration agreement with Vertex to research, develop and commercialize new treatments aimed at the underlying genetic causes of human diseases, including beta thalassemia and sickle cell. In December 2017, we entered into the JDA with Vertex, initially for the development and commercialization of CTX001 for beta thalassemia and sickle cell disease. In addition, in December 2015, we entered into an agreement with Bayer Healthcare to create a joint venture to discover and commercialize therapeutics for the treatment of blood disorders, blindness and heart disease in addition to select indications related to other sensory organs, metabolic diseases and autoimmune diseases based on our CRISPR/Cas9 gene editing technology.

We and Bayer Healthcare each hold a 50% interest in the joint venture and each have two designees on the management board. As such, we cannot control all aspects of the clinical development and commercialization of any product candidate developed by the joint venture. Similarly, under our collaboration agreement with Vertex, Vertex has sole authority to select genetic targets to pursue and we will not have control over the development of any product candidates for the selected genetic targets. Under the JDA, we and Vertex have an equal number of representatives on the various committees contemplated by the JDA, which will prevent us from having sole control of the development of CTX001 or any future product candidates subject to the JDA. Furthermore, pursuant to the JDA, Vertex will be solely responsible for the commercialization activities of any approved products subject to the JDA outside of the United States. Our lack of control over the clinical development and commercialization activities in our agreements with Bayer Healthcare and Vertex could cause delays or other difficulties in the development and commercialization of product candidates, which may prevent among other things, completion of intended IND filings for our hemoglobinopathy programs in a timely fashion, if at all, or the completion or delay in BLA filings, as well as the timely initiation of clinical trials for beta thalassemia upon approval of the CTA, if at all.

In addition, the termination of our agreements with Vertex would prevent us from receiving any milestone, royalty payments and other benefits under that agreement. The termination of our joint venture with Bayer Healthcare would prevent us from participating in the profits of the joint venture. Either occurrence would have a materially adverse effect on our results of operations.

We May Seek To Establish Additional Collaborations And, If We Are Not Able To Establish Them On Commercially Reasonable Terms, We May Have To Alter Our Development And Commercialization Plans.

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

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for any additional collaborations will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing drugs, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. The terms of any additional collaborations or other arrangements that we may establish may not be favorable to us.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, we have granted exclusive rights to Vertex for certain genetic targets, and during the term of the collaboration agreement, we will be restricted from granting rights to other parties to use our gene-editing technology to pursue therapies that address these genetic targets. Similarly, pursuant to our joint venture agreement with Bayer Healthcare, during the term

of the joint venture, and for a specified period after the termination of the joint venture, we will be prohibited from developing products that use our gene-editing technology in specified fields that would compete with the joint venture and Bayer, respectively. The non-competition provisions in each of these agreements could limit our ability to enter into strategic collaborations with future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. If we are unable to negotiate and enter into new collaborations, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization 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 increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

We Expect To Rely On Third Parties To Conduct Our Clinical Trials And Certain Aspects Of Our Preclinical Studies For Our Product Candidates. If These Third Parties Do Not Successfully Carry Out Their Contractual Duties, Comply With Regulatory Requirements Or Meet Expected Deadlines, We May Not Be Able To Obtain Regulatory Approval For Or Commercialize Our Product Candidates And Our Business Could Be Substantially Harmed.

We expect to rely on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct future clinical trials and we currently rely on third parties to conduct certain aspects of our preclinical studies for our product candidates. Nevertheless, we are responsible for ensuring that each of our preclinical studies and any future clinical trials we sponsor are conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards and our reliance on CROs will not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with regulations, commonly referred to as Good Clinical Practices, or GCPs, for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity, and civil and criminal sanctions. For any violations of laws and regulations during the conduct of our preclinical studies and clinical trials, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

We and our CROs will be required to comply with regulations, including GCPs, for conducting, monitoring, recording and reporting the results of preclinical studies and clinical trials to ensure that the data and results are scientifically credible and accurate and that the trial patients are adequately informed, among other things, of the potential risks of participating in clinical trials and their rights are protected. These regulations are enforced by FDA, the Competent Authorities of the Member States of the European Economic Area and comparable health regulatory authorities for any drugs in clinical development. The FDA enforces GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and FDA or comparable health regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our future clinical trials will comply with GCPs. In addition, our future clinical trials must be conducted with product candidates produced in accordance with the requirements in cGMP regulations. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action.

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

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;

- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

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

We Expect To Rely 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. 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.

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 to manufacture supplies and process our product candidates in connection with any clinical trial we undertake of such product candidates. We have not yet caused any product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of 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 and effective.

The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA, or other health regulatory agencies in other jurisdictions, pursuant to inspections that will be conducted after we submit an application to the FDA or other health regulatory agencies. We will not control the manufacturing process of, and will be completely dependent on, our contract manufacturing partners for compliance with regulatory requirements, known as cGMP requirements, for manufacture 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 direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable health 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.

Our Relationships With Healthcare Providers, Physicians, And Third-party Payors Will Be Subject To Applicable Anti-kickback, Fraud And Abuse And Other Healthcare Laws And Regulations, Which Could Expose Us To Criminal Sanctions, Civil Penalties, Exclusion From Government Healthcare Programs, Contractual Damages, Reputational Harm And Diminished Profits And Future Earnings.

Although we do not currently have any drugs on the market, once we begin commercializing our product candidates, if ever, we will be subject to additional healthcare statutory and regulatory requirements and enforcement by the U.S. federal government and states as well as other national, regional or local governments in other jurisdictions in which we conduct our business.

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

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order, or recommendation of, any good or service, for which payment may be made under a state or Federal healthcare program, such as Medicare and Medicaid. 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. Violation of the statute may give rise to criminal and/or civil penalties;
- the federal civil and criminal false claims laws, including the civil False Claims Act, impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval from

Medicare, Medicaid, or other government payors that are false, fictitious or fraudulent or knowingly making, using or causing to be made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false of fraudulent claim for purposes of the False Claims Act;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as further amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations which impose certain requirements on covered entities, including healthcare providers, health plans and healthcare clearing houses, as well as their business associates that perform certain services with respect to safeguarding the privacy, security and transmission of individually identifiable health information that constitutes protected health information, including mandatory contractual terms and restrictions on the use and/or disclosure of such information without appropriate authorization;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the federal physician payment transparency requirements, sometimes referred to as the “Sunshine Act” under the Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children’s Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; and
- analogous laws and regulations in U.S. states, and in other countries, regions or localities in which we may do business, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

On January 31, 2019 the Department of Health and Human Services (HHS) and HHS Office of Inspector General (OIG) proposed an amendment to one of the existing Anti-Kickback safe harbors (42 C.F.R. 1001.952(h)) which would prohibit certain pharmaceutical manufacturers from offering rebates to pharmacy benefit managers (“PBMs”) in the Medicare Part D and Medicaid managed care programs. The proposed amendment would remove protection for "discounts" from Anti-Kickback enforcement action, and would include criminal and civil penalties for knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or reward the referral of business reimbursable under federal health care programs. At the same time, HHS also proposed to create a new safe harbor to protect point-of-sale discounts that drug manufacturers provide directly to patients, and adds another safe harbor to protect certain administrative fees paid by manufacturers to PBMs. If this proposal is adopted, in whole or in part, it could affect the pricing and reimbursement for any products for which we receive approval in the future.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the laws described above or any other government regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from participation in government health care programs, such as Medicare and Medicaid, imprisonment, and the curtailment or restructuring of our operations, any of which could adversely affect our business, financial condition, results of operations, and prospects.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order, or use of medicinal products is prohibited in the European Union. The provision of benefits or advantages to physicians is also governed by the national anti-bribery laws of European Union Member States, such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain European Union Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician’s employer, his or her competent professional organization, and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the national laws, industry codes, or professional codes of conduct applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines, or imprisonment.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply

with current or future statutes, regulations, or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including activities that may be conducted by sales and marketing team we establish, are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil, or administrative sanctions, including exclusions from government funded healthcare programs. Liabilities they incur pursuant to these laws could result in significant costs or an interruption in operations, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Risks Related to Employee Matters, Managing Growth and Other Risks Related to Our Business

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, commercial and business development expertise of Dr. Samarth Kulkarni, our Chief Executive Officer, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment agreements 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. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. The loss of the services of our executive officers or other key employees or consultants could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. If we are unable to retain high quality personnel, our ability to pursue our growth strategy will be limited.

We will also need to recruit and retain qualified scientific, clinical and commercial personnel as we advance the development of our product candidates and product pipeline. We may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific, clinical and commercial personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

In addition, being domiciled and organized in Switzerland may restrict our ability to attract, motivate and retain the required level of qualified personnel. In Switzerland, in 2013 legislation was adopted affecting compensation payable by public companies to members of its board of directors and executive team. Among other things, such legislation (i) imposes an annual binding shareholders' "say on pay" vote with respect to the compensation of executive management, including executive officers and the board of directors; (ii) prohibits severance, advances, transaction premiums and similar payments to executive officers and directors; and (iii) requires companies to specify various compensation-related matters in their articles of association, thus requiring them to be approved by a shareholders' vote.

We Will Need To Develop And Expand Our Company, And We May Encounter Difficulties In Managing This Development And Expansion, Which Could Disrupt Our Operations.

As of December 31, 2018, we had 188 full-time employees and we expect to increase our number of employees and the scope of our operations in 2019 and beyond as we conduct activities as a public company and seek to advance development and if successful, commercialization, of our product candidates. To manage our anticipated development and expansion, 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. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these expansion activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

Our Employees, Principal Investigators, Consultants And Commercial Partners May Engage In Misconduct Or Other Improper Activities, Including Non-compliance With Regulatory Standards And Requirements And Insider Trading.

We are exposed to the risk of fraud or other misconduct by our employees, consultants, and commercial partners, and, if we commence clinical trials, our principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union and other jurisdictions, provide accurate information to the FDA, the European Commission, and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and in other jurisdictions, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or

interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person 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, financial condition, results of operations, and prospects, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

If We Fail To Comply With Environmental, Health And Safety Laws And Regulations, We Could Become Subject To Fines Or Penalties Or Incur Costs That Could Harm Our Business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We contract 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 anticipate obtaining product liability insurance coverage in advance of the commencement of any clinical trial of our product candidates, it may not be adequate to cover all liabilities that we may incur. Further, we anticipate that we will need to increase our insurance coverage if we successfully commercialize any product candidate. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

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

Product Liability Lawsuits Against Us Could Cause Us To Incur Substantial Liabilities And Could Limit Commercialization Of Any Product Candidates That We May Develop.

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

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

Although we anticipate obtaining product liability insurance coverage in advance of the commencement of any clinical trial of our product candidates, it may not be adequate to cover all liabilities that we may incur. Further, we anticipate that we will need to increase our insurance coverage if we successfully commercialize any product candidate. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

If We Fail To Establish And Maintain Proper And Effective Internal Control Over Financial Reporting, Our Operating Results And Our Ability To Operate Our Business Could Be Harmed.

Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that needs to be re-evaluated frequently. We are required to comply with the requirements of The Sarbanes-Oxley Act of 2002, which requires that we maintain effective internal control over financial reporting and disclosure controls and procedures. In particular, we must perform system and process evaluation, document our controls and perform testing of our key control over financial reporting to allow management and our independent public accounting firm to report on the effectiveness of our internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. Our testing, or the subsequent testing by our independent public accounting firm, may reveal deficiencies in our internal control over financial reporting that are deemed to be material weaknesses. If we are not able to comply with the requirements of Section 404 in a timely manner, or if we or our accounting firm identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock would likely decline and we could be subject to lawsuits, sanctions or investigations by regulatory authorities, which would require additional financial and management resources.

We continue to invest in more robust technology and in more resources in order to manage those reporting requirements. Implementing the appropriate changes to our internal controls may distract our officers and employees, result in substantial costs if we implement new processes or modify our existing processes and require significant time to complete. Any difficulties or delays in implementing these controls could impact our ability to timely report our financial results. In addition, we currently rely on a manual process in some areas which increases our exposure to human error or intervention in reporting our financial results. For these reasons, we may encounter difficulties in the timely and accurate reporting of our financial results, which would impact our ability to provide our investors with information in a timely manner. As a result, our investors could lose confidence in our reported financial information, and our stock price could decline.

In addition, any such changes do not guarantee that we will be effective in maintaining the adequacy of our internal controls, and any failure to maintain that adequacy could prevent us from accurately reporting our financial results.

We May Fail To Comply With Evolving European And Other Privacy Laws.

We currently conduct clinical trials in the European Economic Area ("EEA"). As a result, we are subject to additional privacy laws. The General Data Protection Regulation, (EU) 2016/679 ("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 United States, 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 limited enforcement of the GDPR to date, we face uncertainty as to the exact interpretation of the new requirements on our trials 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 addition, we must also ensure that we maintain adequate safeguards to enable the transfer of personal data outside of the EEA, in particular to the United States, 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.

Our Internal Computer Systems, Or Those Of Our Collaborators Or Other Contractors Or Consultants, May Fail Or Suffer Security Breaches, Which Could Result In A Material Disruption Of Our Product Development Programs.

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. 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.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company and our vendors, including personal information of our employees and study subjects, and company and vendor confidential data. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our personnel or the personnel of our vendors to disclose sensitive information in order to gain access to our data and/or systems. We may experience threats to our data and systems, including malicious codes and viruses, phishing and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our information technology systems or those of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. In addition, we could be subject to regulatory actions and/or claims made by individuals and groups in private litigation involving privacy issues related to data collection and use practices and other data privacy laws and regulations, including claims for misuse or inappropriate disclosure of data, as well as unfair or deceptive practices. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become increasingly sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely. As we outsource more of our information systems to vendors, engage in more electronic transactions with payors and patients, and rely more on cloud-based information systems, the related security risks will increase and we will need to expend additional resources to protect our technology and information systems. In addition, there can be no assurance that our internal information technology systems or those of our third-party contractors, or our consultants' efforts to implement adequate security and control measures, will be sufficient to protect us against breakdowns, service disruption, data deterioration or loss in the event of a system malfunction, or prevent data from being stolen or corrupted in the event of a cyberattack, security breach, industrial espionage attacks or insider threat attacks which could result in financial, legal, business or reputational harm.

Our Business Is Subject To Economic, Political, Regulatory And Other Risks Associated With International Operations.

Our business is subject to risks associated with conducting business internationally. We and a number of our suppliers and collaborative and clinical study relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing regulatory requirements for drug approvals in non-U.S. countries;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with non-U.S. laws and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates and currency controls;
- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or non-U.S. governments;

- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling outside the United States;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities outside the United States;
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including floods and fires; and
- adverse effects and instability in global financial markets, political institutions and regulatory agencies resulting from the United Kingdom's June 23, 2016 vote to leave the European Union and subsequent invocation of Article 50 of the Lisbon Treaty on March 29, 2017.

Legal, political and economic uncertainty surrounding the planned exit of the U.K. from the European Union, or EU, may be a source of instability in international markets, create significant currency fluctuations, adversely affect our operations in the U.K. and pose additional risks to our business, revenue, financial condition, and results of operations.

On June 23, 2016, the U.K. held a referendum in which a majority of the eligible members of the electorate voted to leave the EU. The U.K's withdrawal from the EU is commonly referred to as Brexit. Pursuant to Article 50 of the Treaty on European Union, the U.K. will cease to be an EU Member State either on the effective date of a withdrawal agreement (entry into a withdrawal agreement will require U.K. parliamentary approval) or, failing that, two years following the U.K.'s notification of its intention to leave the EU, unless the European Council (together with the U.K.) unanimously decides to extend this two year period. On March 29, 2017, the U.K. formally notified the European Council of its intention to leave the EU. The U.K. is therefore scheduled to leave the EU at 11:00p.m. GMT on March 29, 2019. It is unclear how long it will take to negotiate a withdrawal agreement, but it appears likely that Brexit will continue to involve a process of lengthy negotiations between the U.K. and EU Member States to determine the future terms of the U.K's relationship with the EU. In March 2018, the U.K reached a provisional agreement with the EU on transitional arrangements following the U.K's exit (which are intended to enable the UK to remain within the EU single market and customs union for a transitional period through 2020), but this agreement needs to be formally agreed as part of the withdrawal agreement currently under negotiation. As of February 2019, this agreement was not formally agreed to by the parties thereto and there is uncertainty as to whether such agreement, or any other agreement regarding the U.K's withdrawal from the EU, will be agreed to before March 29, 2019.

The lack of clarity on future U.K. laws and regulations (including financial laws and regulations, tax and free trade agreements, intellectual property rights, data protection laws, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws) may negatively impact foreign direct investment in the U.K., increase costs, depress economic activity and restrict access to capital.

The uncertainty concerning the U.K's legal, political and economic relationship with the EU after Brexit 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) beyond the date of Brexit.

These developments, or the perception that any of them could occur, may have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and limit the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility.

If the U.K. and the EU are unable to negotiate acceptable withdrawal terms or if other EU Member States pursue withdrawal, barrier-free access between the UK and other EU Member States or among the European Economic Area overall could be diminished or eliminated. The long-term effects of Brexit will depend on any agreements (or lack thereof) between the U.K. and the EU and, in particular, any arrangements for the U.K. to retain access to EU markets either during a transitional period or more permanently.

Such a withdrawal from the EU is unprecedented, and it is unclear how the U.K's access to the European single market for goods, capital, services and labor within the EU, or single market, and the wider commercial, legal and regulatory environment, will impact our current and future operations (including business activities conducted by third parties and contract manufacturers on our behalf) and clinical activities (including, without limitation, clinical activities for CTX001) in the U.K. In addition to the foregoing,

our U.K. operations support our current and future operations and clinical activities (including, without limitation, clinical activities for CTX001) in other countries in the EU and European Economic Area, or EEA, and these operations and clinical activities could be disrupted by Brexit.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of the U.K's withdrawal from the EU, the U.K. could lose the benefits of global trade agreements negotiated by the EU on behalf of its members, which may result in increased trade barriers that could make our doing business in the EU and the EEA more difficult. Furthermore, at present, there are no indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the U.K., or what, if any, role the EMA may have in the approval process. Even prior to any change to the U.K's relationship with the EU, the announcement of Brexit has created economic uncertainty surrounding the terms of Brexit and its consequences could adversely impact customer confidence resulting in customers reducing their spending budgets on our solutions, which could adversely affect our business, revenue, financial condition, results of operations and could adversely affect the market price of our common shares.

Our Business Operations Have a Substantial International Footprint and We May Further Expand In The Future, Which Presents Challenges In Managing Our Business Operations.

We are headquartered in Zug, Switzerland and have offices in the U.S. and the United Kingdom. In addition, we may expand our international operations into other countries in the future. While we have acquired significant management and other personnel with substantial experience, conducting our business in multiple countries subjects us to a variety of risks and complexities that may materially and adversely affect our business, results of operations, financial condition and growth prospects, including, among other things:

- the increased complexity and costs inherent in managing international operations;
- diverse regulatory, financial and legal requirements, and any future changes to such requirements, in one or more countries where we are located or do business;
- country-specific tax, labor and employment laws and regulations;
- challenges inherent in efficiently managing employees in diverse geographies, including the need to adapt systems, policies, benefits and compliance programs to differing labor and other regulations;
- liabilities for activities of, or related to, our international operations or product candidates;
- changes in currency rates; and
- regulations relating to data security and the unauthorized use of, or access to, commercial and personal information.

As we continue to expand our operations, our corporate structure and tax structure has become substantially more complex. In connection with our current and future potential partnerships, we are actively engaged in developing and applying technologies and intellectual property with a view toward commercialization of products globally, often with commercialization partners. In connection with those activities, we already have and will likely continue to engage in complex cross-border and global transactions involving our technology, intellectual property and other assets, between CRISPR and other entities such as partners and licensees, and between companies within the CRISPR group. Such cross-border and global arrangements are both difficult to manage and can potentially give rise to complexities in areas such as tax treatment, particularly since we are subject to multiple tax regimes and different tax authorities can also take different views from each other, even as regards the same cross-border transaction or arrangement. There can be no assurance that we will effectively manage this increased complexity without experiencing operating inefficiencies, control deficiencies or tax liabilities. Significant management time and effort is required to effectively manage the increased complexity of our company, and our failure to successfully do so could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Risks Related to Intellectual Property

If We Are Unable To Obtain Or Protect Intellectual Property Rights Related to Our Proprietary Gene-Editing Technology And Product Candidates, We May Not Be Able To Compete Effectively In Our Markets.

Our success depends in large part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other jurisdictions with respect to our CRISPR/Cas9 platform technology and any proprietary product candidates and technology we develop. We rely upon a combination of intellectual property rights, including patent rights, trade secret protection and confidentiality agreements to protect the intellectual property related to our gene-editing technology and product candidates. Presently we have rights to certain intellectual property, through licenses from third parties and under patent rights that we own, to develop our gene-editing technology and/or product candidates. For example, through our 2014 exclusive license with Dr. Charpentier, we exclusively license the Patent Portfolio which covers various aspects of our gene-editing technology, including, for example, 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 worldwide patent portfolio as the "Patent Portfolio". This patent portfolio to-date includes, for example, twenty-six (26) granted or allowed patents in the United States, United Kingdom, Europe, Japan, China, Ukraine, New Zealand, Singapore, Australia, Mexico, Tunisia, Hong Kong, Israel and South Africa and pending patent applications in the United States, Europe, Canada, Mexico, Australia and other selected countries in Central America, South America, Asia and Africa. In addition, we have filed numerous patent applications covering our product candidates.

We seek to protect our proprietary position by in-licensing intellectual property to cover our platform technology and filing patent applications in the United States and in other jurisdictions related to our technologies and product candidates that are important to our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position. If we or our licensors are unable to obtain or maintain patent protection with respect to our CRISPR/Cas9 platform technology and any proprietary products and technology we develop, our business, financial condition, results of operations and prospects could be materially harmed.

However, the strength of patents in the biotechnology and pharmaceutical field generally, and the genome-editing field in particular, involves complex legal and scientific questions and can be uncertain and we cannot offer any assurances about which, if any, patent rights that we own or in-license will issue, the breadth of any such patent rights or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. For example, the scope of patent protection that will be available to us in the United States and in other countries is uncertain. Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our intellectual property, obtain, maintain, defend and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our owned and licensed patents. With respect to both in-licensed and owned intellectual property, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors, or if any such patents will be found invalid, unenforceable or not infringed if challenged by our competitors.

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with any degree of certainty whether the inventors of our licensed patents and applications were the first to make the inventions claimed in our owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Moreover, there is no assurance that all of the potentially relevant prior art relating to our owned and in-licensed patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application.

The ultimate outcome of any pending or allowed patent application we file is uncertain and the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we license or own currently or in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage.

Additionally, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability and our patents may be challenged in the courts or patent offices in the United States and in other jurisdictions. We may be subject to a third party preissuance submission of prior art to the USPTO, or a patent office in another jurisdiction, or become involved in opposition, derivation, revocation, reexamination, post-grant review and inter partes review, or interference proceedings, or litigation challenging our patent rights or the patent rights of others. Indeed, certain of our fundamental intellectual property has been subject to third party observations and oppositions outside the United States and interference proceedings within the United States. 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 gene-editing technology and/or product candidates. It is possible that we have failed to identify relevant third-party patents or applications. Thus, there is no assurance that all of the potentially relevant prior art relating to our, or our in-licensed patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Competitors may also claim that they invented the inventions claimed in such issued patents or patent applications prior to our inventors, or may have filed patent applications before our inventors did. A competitor may also claim that our products and services infringe its patents and that we therefore cannot practice our technology as claimed under our patent applications, if issued. An adverse determination in any such claim may result in our inability to manufacture or commercialize products without infringing third-party patent rights. Competitors may also contest our patents, if issued, by showing that the invention was not patent-eligible, was not novel, was obvious or that the patent claims failed any other requirement for patentability. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights or allow third parties to commercialize our technology or products and compete directly with us, without payment to us.

Moreover, we, or one of our licensors, may have to participate in additional interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a non-U.S. patent office, that challenge priority of invention or other features of patentability. Such challenges may result in loss of patent rights, loss of exclusivity or freedom to operate, or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. In addition, if the breadth or strength of protection provided by our owned and in-licensed patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Further, even if they are unchallenged, our owned and in-licensed patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. Consequently, we do not know whether any of our genome-editing platform advances and product candidates will be protectable or remain protected by valid and enforceable patents. For example, our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. For example, we are aware that third parties have suggested the use of the CRISPR technology in conjunction with a protein other than Cas9. Our owned and in-licensed patents may not cover such technology. If our competitors commercialize the CRISPR technology in conjunction with a protein other than Cas9, our business, financial condition, results of operations, and prospects could be materially adversely affected.

Because our gene-editing technology and product candidates could require the use of proprietary rights held by third parties, the growth of our business could depend in part on our ability to acquire, in-license, or use these proprietary rights. We may be unable to acquire or in-license such intellectual property rights from third parties that we identify. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. Furthermore, 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 gene-editing technology, product candidates or the use of such product candidates do not infringe third-party patents. 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.

Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business. If the patent rights we own or have in-licensed fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for either our gene-editing technology and/or product candidates, it could threaten our ability to commercialize future products, or dissuade companies from collaborating with us to develop current or future product candidates.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, 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 United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Our Rights To Develop And Commercialize Our Technology And Product Candidates Are Subject, In Part, To The Terms And Conditions Of Licenses Granted To Us By Others.

We are reliant upon licenses to certain intellectual property from third parties that are important or necessary to the development of our gene-editing technology and product candidates. These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use or cover all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses.

Moreover, under our in-license agreements, including our 2014 exclusive license agreement with Dr. Emmanuelle Charpentier, we will be required to pay royalties based on our revenues from sales of our products utilizing the licensed technologies and these royalty payments could adversely affect the overall profitability for us of any products that we may seek to commercialize. Under each of our in-license agreements with, Dr. Charpentier, we have an obligation to use commercially reasonable efforts to develop and obtain regulatory approval to market a licensed therapeutic product. Our in-license agreements with Dr. Charpentier also include an obligation to file a U.S. Investigational New Drug application (or its equivalent in a major market country) by April 2021 and an obligation to file a U.S. Investigational New Drug application (or its equivalent in a major market country) by April 2024. We may not be successful in meeting these obligations in the future on a timely basis or at all. Our failure to meet these obligations may give Dr. Charpentier the right to terminate our license rights. We will need to outsource and rely on third parties for many aspects of the clinical development of the products covered under our license agreements. Delay or failure by these third parties could adversely affect our ability to meet our diligence obligations and the continuation of our license agreements with third-party licensors.

In spite of our best efforts, our licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. In addition, we may seek to obtain additional licenses from our licensors and, in connection with obtaining such licenses, we may agree to amend our existing licenses in a manner that may be more favorable to the licensors, including by agreeing to terms that could enable third parties (potentially including our competitors) to receive licenses to a portion of the intellectual property that is subject to our existing licenses. Any of these events could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Some Of Our Own and In-licensed Patents Rights Were and May Be Subject To Inter Partes Administrative Proceedings. Our Owned And In-Licensed Patents And Other Intellectual Property May Be Subject To Further Such Proceedings. If We Or Our Licensors Are Unsuccessful In Any Of These Proceedings, We May Be Required To Obtain Licenses From Third Parties, Which May Not Be Available On Commercially Reasonable Terms Or At All, Or To Cease The Development, Manufacture, And Commercialization Of One Or More Of The Product Candidates We May Develop, Which Could Have A Material Adverse Impact On Our Business.

The Broad owns a patent family that includes issued patents in the U.S. and Europe that claim certain aspects of CRISPR/Cas9 systems to edit DNA in eukaryotic cells, including human cells (collectively, the Broad Institute Patent Family). In January 2016, an interference proceeding was declared in the U.S. Patent and Trademark Office (USPTO) between the claims from one Patent Portfolio patent application and certain U.S. patents and one application of the Broad Institute Patent Family to determine which set of inventors invented first and, thus, is entitled to patents on the invention in the U.S. Following motions by the parties and other procedural matters, the PTAB concluded in early 2017 that the declared interference should be discontinued without deciding who was first to invent. In its decision, the PTAB concluded that the claim sets presented by the two parties were considered patentably distinct from each other because the involved CVC patent application's claims were broader in scope in that they were not restricted to use in eukaryotic cells, whereas Broad's claims were so limited. The PTAB did not make any decision regarding inventorship or priority, and therefore ownership, of the inventions claimed by the patents and applications at issue. In April 2017, CVC appealed the PTAB decision to the Federal Circuit, asking it to review and reverse the PTAB's February 2017 decision. The Federal Circuit conducted a hearing on the appeal on April 30, 2018, and on September 10, 2018, affirmed the PTAB's decision to terminate the interference proceeding. Because the Patent Portfolio and the Broad Institute patent family both allege owning intellectual property claiming overlapping aspects of CRISPR/Cas9 systems and methods to edit DNA 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.

In addition to the Broad, other third parties including for example Vilnius University, ToolGen, Inc., MilliporeSigma (a subsidiary of Merck KGaA) and Harvard University, have filed patent applications claiming CRISPR/Cas9-related inventions around or within a year after the first CVC patent application within the Patent Portfolio was filed and may allege that they invented one or more of the inventions claimed by the Patent Portfolio before CVC. CVC continues to prosecute other patent claims covering the CRISPR/Cas9 inventions, which could also result in allowable or issued patents in the U.S. Certain of the claims being prosecuted by CVC, if found allowable by the USPTO, could lead to interference proceedings against patents or patent applications owned by other parties, including the Broad Institute Patent Family, with respect to certain claims expressly relating to the use of CRISPR/Cas9 in eukaryotic cells. If the USPTO deems the scope of the claims of one or more of these parties to sufficiently overlap with the allowable claims from a patent or patent application within the Patent Portfolio, the USPTO could declare other interference proceedings to determine the first inventor of such claims. We cannot be certain which of these results, if any, will actually occur. Further, the effects that any such results may have on us and our intellectual property position are currently unknown. The Broad, as well as other third parties, 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, CVC or the other third parties could seek judicial review of their inventorship claims. If CVC fails 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.

Further, Broad, Toolgen Inc., Vilnius University, Harvard University, MilliporeSigma (a subsidiary of Merck KGaA), and other parties routinely file international counterparts of their U.S. applications, some of which have been granted or could in the future be granted in Europe and/or other non-U.S. jurisdictions. We and third parties have initiated opposition proceedings against some of these grants, and we may in the future oppose other grants to these or other applicants. Similarly, our intellectual property is and may in the future become involved in opposition proceedings in Europe or other jurisdictions. For example, two of our in-licensed granted European patents have been opposed by multiple third parties. These oppositions could lead to the revocation of the patents in whole or in part, or could lead to the claims being narrowed in a way that could impair or preclude our ability to enforce the patents against competitors in Europe.

If we or our licensors are unsuccessful in any interference proceedings or other priority or validity disputes (including any patent oppositions) to which we or they are subject or become subject to, we may lose valuable intellectual property rights through the loss or narrowing of one or more of our patents and/or patent applications. If we or our licensors are unsuccessful in any interference proceeding or other dispute, we may be required to seek to obtain and maintain licenses from third parties, including parties involved in any such interference proceedings or other disputes. These third parties would be under no obligation to grant to us any such license and such licenses may not be available on commercially reasonable terms or at all, or may be non-exclusive. If we are unable to obtain and maintain such licenses, we and our partners may need to cease the practice of our core gene editing, and the development, manufacture, and commercialization of one or more of the product candidates we may develop. The loss of exclusivity or the narrowing of our patent claims could limit our ability to stop others from using or commercializing similar or identical technology and products. Any of the foregoing could result in a material adverse effect on our business, financial condition, results of operations, or prospects. If we are unsuccessful in a dispute with Broad, for example, then we and our partners may be blocked from commercializing any products based on our core gene editing technology. Even if we are successful in an interference proceeding or other similar disputes, it could result in substantial costs and be a distraction to management and other employees.

The Intellectual Property That Protects Our Core Gene Editing Technology Is Jointly Owned, And Our License Is From Only One Of The Joint Owners, Materially Limiting Our Rights In The United States And In Other Jurisdictions

The Patent Portfolio we have exclusively licensed from Dr. Charpentier is the core patent protection for our gene editing technology. However, that family includes other named inventors who assigned their rights either to California or to Vienna. As such, the Patent Portfolio is currently co-owned by Dr. Charpentier, California, and Vienna. On December 15, 2016, we entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement, or IMA, with California, Vienna and their licensees including Caribou and Caribou's licensee Intellia. Under the IMA, the co-owners provided reciprocal worldwide cross-consents to each of the other co-owners' licensees and sublicensees, and agreed to a number of other commitments and obligations with respect to supporting and managing the underlying CRISPR/Cas9 gene editing intellectual property, including a cost-sharing agreement. As explained more fully below, that leaves us in a position of holding only non-exclusive or co-exclusive rights to the patent rights that protect our core gene editing technology, and we must continue to satisfy our contractual obligations under the IMA in order to maintain the effectiveness of the consents by California and Vienna to our license from Dr. Charpentier.

In the United States, each co-owner has the freedom to license and exploit the technology. As a result, we do not have exclusive access to any intellectual property rights that Dr. Charpentier co-owns with another entity, such as California and Vienna. Our license with Dr. Charpentier is therefore non-exclusive with respect to such co-owned rights. Furthermore, in the United States each co-owner is required to be joined as a party to any claim or action we may wish to bring to enforce those patent rights. Moreover, in the United States, non-exclusive licenses have no standing to bring a patent infringement action before a court. Therefore, for the patents owned with California and Vienna we have no ability to pursue third party infringement claims without cooperation of California and Vienna and potentially their licensees. Although we have entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement with Vienna and California and their licensees, which provides for, among other things, notice of and coordination in the event of third-party infringement of the patent rights within the Patent Portfolio, there can be no assurance that Vienna and California will cooperate with us in any future infringement. If we are unable to enforce our core patent rights licensed from Dr. Charpentier, we may be unable to prevent third parties from competing with us and may be unable to persuade companies to sublicense our technology, either of which could have a material adverse effect on our business.

If We Experience Disputes With The Third Parties That We In-license Intellectual Property Rights From, We Could Lose License Rights That Are Important To Our Business

We license the intellectual property that covers our gene-editing technology from a third party, and we expect to continue to in-license additional third-party intellectual property rights as we expand our gene-editing technology. Disputes may arise with the third parties from whom we license our intellectual property rights from for a variety of reasons, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships and obligations associated with sublicensing;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, the agreements under which we currently license intellectual property or technology from third parties, or maintain consents under the IMA, are complex, and certain provisions in such agreements may be susceptible to multiple interpretations, or may conflict in such a way that puts us in breach of one or more agreements, which would make us susceptible to lengthy and expensive disputes with one or more of our licensing partners or the parties to the IMA. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or

technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

We May Not Be Successful In Obtaining Necessary Rights To Any Product Candidates We May Develop Through Acquisitions And In-licenses.

We currently have rights to intellectual property, through in-licenses from third parties, to identify and develop product candidates. Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of gene-editing technology and filing patent applications potentially relevant to our business. For example, we are aware of several third-party patent applications that, if issued, may be construed to cover our gene-editing technology and product candidates. In order to avoid infringing these third-party patents, we may find it necessary or prudent to obtain licenses from such third party intellectual property holders. We may also require licenses from third parties for certain modified or improved components of gene-editing technology, such as modified nucleic acids, as well as non-CRISPR/Cas9 technologies such as delivery methods that we are evaluating for use with product candidates we may develop. In addition, with respect to any patents we co-own with third parties, we may require licenses to such co-owners' interest to such patents. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for product candidates we may develop and gene-editing technology. The licensing or acquisition of third party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, or discontinue the practice of our core CRISPR/Cas9 gene-editing technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Issued Patents Covering Our Technology And Product Candidates Could Be Found Invalid Or Unenforceable If Challenged In Court.

If we or one of our licensors initiated legal proceedings against a third party to enforce a patent covering a product candidate we may develop or our technology, including CRISPR/Cas9, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution.

Third parties have raised challenges to the validity of certain of our in-licensed patent applications, such as our in-licensed CRISPR/Cas9 patent applications in the context of third party observations and oppositions filed in Europe and Australia, and may in the future raise similar claims before administrative bodies in the United States or in other jurisdictions, even outside the context of litigation. Mechanisms for challenging the validity of patents in patent offices include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in non-U.S. jurisdictions (e.g., opposition proceedings). Such proceedings could – after exhausting available appeals – result in the loss of our patent applications or patents, or their narrowing in such a way that they no longer cover our technology or platform, or any product candidates that we may develop. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our technology or platform, or any product candidates that we may develop. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations, and prospects.

The Intellectual Property Landscape Around Gene-Editing Technology, Including CRISPR/Cas9, Is Highly Dynamic, And Third Parties May Initiate And Prevail In Legal Proceedings Alleging That The Patents That We In-License Or Own Are Invalid Or That We Are Infringing, Misappropriating, Or Otherwise Violating Their Intellectual Property Rights, The Outcome Of Which Would Be Uncertain And Could Have A Material Adverse Effect On The Success Of Our Business.

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market, and sell any product candidates that we may develop and use our proprietary technologies without infringing, misappropriating, or otherwise violating the intellectual property and proprietary rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. We are subject to and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our technology and any product candidates we may develop, including re-examination interference proceedings, post-grant review, *inter partes* review, and derivation proceedings before the USPTO and similar proceedings in other jurisdictions such as oppositions before the European Patent Office. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. We are aware of certain third-party patents and patent applications including, for example, the Broad, Vilnius, Harvard and Sigma-Aldrich patents described above. If we are unable to prove that these patents are invalid and we are not able to obtain or maintain a license on commercially reasonable terms, such patents could have a material adverse effect on the conduct of our business. If we are found to infringe such third-party patents, we and our partners may be required to pay damages, cease commercialization of the infringing technology, including our core CRISPR/Cas9 gene-editing technology, or obtain a license from such third parties, which may not be available on commercially reasonable terms or at all. Additionally, we have not performed any freedom-to-operate analysis on specific product candidates at this stage to identify potential infringement risks. A proper analysis of that type will not be feasible until specific product candidates are designed.

Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, enforceability, ownership, or priority. A court of competent jurisdiction could hold that these third-party patents are valid, enforceable, and infringed, which could materially and adversely affect our ability to commercialize any product candidates we may develop and any other product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe a third party's intellectual property rights, and we are unsuccessful in demonstrating that such patents are invalid or unenforceable, we could be required to obtain a license from such third party to continue developing, manufacturing, and marketing any product candidates we may develop and our technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We also could be forced, including by court order, to cease developing, manufacturing, and commercializing the infringing technology or product candidates. In addition, we could be found liable for significant monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar material adverse effect on our business, financial condition, results of operations, and prospects.

Intellectual Property Litigation Could Cause Us To Spend Substantial Resources And Distract Our Personnel From Their Normal Responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable and generally expensive and time-consuming and is likely to divert significant resources from our core business, including distracting our technical and management personnel from their normal responsibilities and generally harm our business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation in certain countries, including the United States, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater

financial resources. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing or misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Obtaining And Maintaining Our Patent Protection Depends On Compliance With Various Procedural, Document Submission, Fee Payment, And Other Requirements Imposed By Government Patent Agencies And Our Patent Protection Could Be Reduced Or Eliminated For Non-compliance With These Requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned or licensed patents and applications. In certain circumstances, we rely on our licensing partners to pay these fees due to U.S. and non-U.S. patent agencies. The USPTO and various non-U.S. government agencies require compliance with several procedural, documentary, fee payment, and other similar provisions during the patent application process. In addition, periodic maintenance fees on issued patents often must be paid to the USPTO and other patent agencies over the lifetime of the patent. We are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in a partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our product candidates, we may not be able to stop a competitor from marketing drugs that are the same as or similar to our product candidates, which would have a material adverse effect on our business.

Some Intellectual Property Which We Have In-licensed May Have Been Discovered Through Government Funded Programs And Thus May Be Subject To Federal Regulations Such As "march-in" Rights, Certain Reporting Requirements And A Preference For U.S.-based Manufacturers. Compliance With Such Regulations May Limit Our Exclusive Rights, And Limit Our Ability To Contract With Non-U.S. Manufacturers.

The intellectual property rights to which we have in-licensed under Dr. Charpentier's joint interest are co-owned by California, which has indicated that one or more of the inventions were made under Grant No. GM081879 awarded by the National Institute of Health. These rights are therefore subject to certain federal regulations. The U.S. government has certain rights pursuant to the Bayh-Dole Act of 1980, or Bayh-Dole Act, to patents covering government rights in certain inventions developed under a government-funded program. These rights include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations, also referred to as "march-in rights." The U.S. government also has the right to take title to these inventions if we, or the applicable contractor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable contractor to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. To the extent any of our current or future patents covering inventions is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

We May Not Be Able To Protect Our Intellectual Property And Proprietary Rights Throughout The World.

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive. The requirements for patentability may differ in certain countries, particularly in developing countries. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in intellectual property laws various jurisdictions worldwide. Additionally, the patent laws of some countries do not afford intellectual property protection to the same extent as the laws of the United States. For example, unlike patent law in the United States, the patent law in Europe and many other jurisdictions precludes the patentability of methods of treatment of the human body and imposes substantial restrictions on the scope of claims it will grant if broader than specifically disclosed embodiments.

Many companies have encountered significant problems in protecting and defending intellectual property rights in various jurisdictions globally. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside

the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property and proprietary rights in various jurisdictions globally could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Changes To The Patent Law In The United States And Other Jurisdictions Could Diminish The Value Of Patents In General, Thereby Impairing Our Ability To Protect Our Product Candidates.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or Leahy-Smith Act, signed into law on September 16, 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. In addition, the Leahy-Smith Act has transformed the U.S. patent system into a "first to file" system. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could harm our business, results of operations and financial condition.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. For example, in *Association for Molecular Pathology v. Myriad Genetics, Inc*., the Supreme Court ruled that a "naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," and invalidated Myriad Genetics' claims on the isolated BRCA1 and BRCA2 genes. Certain claims of our patents relate to CRISPR/Cas9 gene-editing technology as well as guide components that are directed to naturally occurring DNA sequences. To the extent that such claims are deemed to be directed to natural products, or to lack an inventive concept above and beyond an isolated natural product, a court may decide the claims are invalid under *Myriad*. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to obtain patent protection for our proprietary technology or our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Europe's planned Unified Patent Court may particularly present uncertainties for our ability to protect and enforce our patent rights against competitors in Europe. While that new court is being implemented to provide more certainty and efficiency to patent enforcement throughout Europe, it will also provide our competitors with a new forum to use to centrally revoke our European patents. It will be several years before we will understand the scope of patent rights that will be recognized and the strength of patent remedies that will be provided by that court. We will have the right to opt our patents out of that system over the first seven years of the court, but doing so may preclude us from realizing the benefits of the new unified court.

Obtaining And Maintaining Our Patent Protection Depends Oon 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.

If We Are Unable To Protect The Confidentiality Of Our Trade Secrets, Our Business And Competitive Position Would Be Harmed.

In addition to seeking patents for some of our technology and product candidates, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary information and to maintain our competitive position. Trade secrets and know-how can be difficult to protect. In particular, we anticipate that with respect to our technology platform, these trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel from academic to industry scientific positions.

We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

If We Do Not Obtain Patent Term Extension And Data Exclusivity For Any Product Candidates We May Develop, Our Business May Be Materially Harmed.

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

Intellectual Property Rights Do Not Necessarily Address All Potential Threats.

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

- others may be able to make gene therapy products that are similar to any product candidates we may develop or utilize similar gene therapy technology but that are not covered by the claims of the patents that we license or may own in the future;

- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

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

We May Be Subject To Claims That Our Employees, Consultants, Or Advisors Have Wrongfully Used Or Disclosed Alleged Trade Secrets Of Their Current Or Former Employers Or Claims Asserting Ownership Of What We Regard As Our Own Intellectual Property.

Many of our employees, consultants, and advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies. Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

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

If Our Trademarks 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 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 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, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our unregistered trademarks. Over the long term, if we are unable to successfully register our trademarks and establish name recognition based on our trademarks, 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 The Ownership of Our Common Shares

We Will Incur Increased Costs As A Result Of Operating As A Public Company And Our Management Will Be Required To Devote Substantial Time To New Compliance Initiatives And Corporate Governance Practices.

As a public company, and particularly now that we are no longer an "emerging growth company," we will incur significant legal, accounting and other expenses that we did not incur as a private company. SOX, 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 towards maintaining compliance with these requirements. Moreover, these requirements have increased our legal and financial compliance costs and have made some activities more time-consuming and costly.

Pursuant to SOX 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. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants, adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by SOX Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

The Market Price Of Our Common Shares Has Been Volatile and Fluctuate Substantially, Which Could Result In Substantial Losses For Shareholders.

Our share price has been and in the future, may be subject to substantial volatility. In addition, the stock market in general, and Nasdaq listed and biopharmaceutical companies in particular have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. For example, our shares traded within a range of a high price of $73.90 and a low price of $11.63 per share for the period beginning on October 19, 2016, our first day of trading on the Nasdaq Global Market, through December 31, 2018. As a result of this volatility, our shareholders could incur substantial losses. In addition, the market price for our common shares may be influenced by many factors, including:

- the success of existing or new competitive products or technologies;
- the timing and results of any product candidates that we may develop;
- commencement or termination of collaborations for our product development and research programs;
- failure or discontinuation of any of our product development and research programs;
- results of preclinical studies, clinical trials, or regulatory approvals of product candidates of our competitors, or announcements about new research programs or product candidates of our competitors;
- developments or changing views regarding the use of genomic products, including those that involve gene editing;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our research programs, clinical development programs, or product candidates that we may develop;
- the results of our efforts to 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;
- announcement or expectation of additional financing efforts;
- sales of our common shares by us, our insiders, or other shareholders;

- expiration of market stand-off or lock-up agreements;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our common shares;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

These and other market and industry factors may cause the market price and demand for our common shares to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from readily selling their common shares and may otherwise negatively affect the liquidity of our common shares. In the past, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our shareholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert the time and attention of our management.

If Securities Analysts Do Not Publish Research Or Reports About Our Business Or If They Publish Negative Evaluations Of Our Common Shares, The Price Of Our Common Shares Could Decline.

The trading market for our common shares will rely in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts covering our business downgrade their evaluations of our common shares, the price of our common shares could decline. If one or more of these analysts cease to cover our common shares, we could lose visibility in the market for our common shares, which in turn could cause our common share price to decline.

Our Executive Officers, Directors, Principal Shareholders And Their Affiliates Maintain The Ability To Exercise Significant Influence Over Our Company And All Matters Submitted To Shareholders For Approval.

The holdings of our executive officers, directors and shareholders who own more than 5% of our outstanding common shares, together with their affiliates and related persons, represent beneficial ownership, in the aggregate, of approximately 27.5% of our common shares, based on the number of common shares outstanding as of February 21, 2019. As a result, these shareholders, if they choose to act together, will be able to influence our management and affairs and the outcome of matters submitted to our shareholders for approval, including the election of directors and any sale, merger, consolidation, or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other shareholders may desire.

In addition, this concentration of ownership might adversely affect the market price of our common shares by:

- delaying, deferring or preventing a change of control of us;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us

We Have Broad Discretion In The Use Of Our Cash Reserves And May Not Use Such Cash Reserves Effectively.

Our management has broad discretion to use our cash reserves and could use our cash reserves in ways that do not improve our results of operations or enhance the value of our common shares. 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 shares to decline, and delay the development of our product candidates. Pending their use, we may invest our cash reserves in a manner that does not produce income or that loses value.

The Market Price Of Our Common Shares May Be Adversely Affected By Market Conditions Affecting The Stock Markets In General, Including Price And Trading Fluctuations On The Nasdaq Global Market.

Market conditions may result in volatility in the level of, and fluctuations in, market prices of stocks generally and, in turn, our common shares and sales of substantial amounts of our common shares in the market, in each case being unrelated or disproportionate to changes in our operating performance. The overall weakness in the economy has recently contributed to the extreme volatility of the markets which may have an effect on the market price of our common shares.

Sales Of A Substantial Number Of Our Common Shares In The Public Market Could Cause Our Share Price To Fall.

Sales of a substantial number of our common shares in the public market or the perception that these sales might occur could depress the market price of our common shares, could make it more difficult for you to sell your common shares at a time and price that you deem appropriate and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common shares.

We Do Not Expect To Pay Dividends In The Foreseeable Future.

We have not paid any dividends since our incorporation. Even if future operations lead to significant levels of distributable profits, we currently intend that any earnings will be reinvested in our business and that no dividends will be paid prior to the time we have an established revenue stream to support continuing dividends. The proposal to pay future dividends to shareholders will in addition effectively be at the discretion of our board of directors and shareholders after taking into account various factors including our business prospects, cash requirements, financial performance and new product development. In addition, payment of future dividends is subject to certain limitations pursuant to Swiss law or by our articles of association. Accordingly, investors cannot rely on dividend income from our common shares and any returns on an investment in our common shares will likely depend entirely upon any future appreciation in the price of our common shares. Dividends, if any, paid on our common shares are subject to Swiss federal withholding tax, except if paid out of reserves from capital contributions ("*Kapitaleinlagen*").

We Are A Swiss Corporation. The Rights Of Our Shareholders May Be Different From The Rights Of Shareholders In Companies Governed By The Laws Of U.S. Jurisdictions.

We are a Swiss corporation. Our corporate affairs are governed by our articles of association and by Swiss law. The rights of our shareholders and the responsibilities of members of our board of directors may be different from the rights and obligations of shareholders and directors of companies governed by the laws of U.S. jurisdictions. In the performance of its duties, our board of directors is required by Swiss law to consider the interests of our Company, our shareholders and our employees with due observation of the principles of reasonableness and fairness. It is possible that the board of directors will consider interests that are different from, or in addition to, your interests as a shareholder. Swiss corporate law limits the ability of our shareholders to challenge resolutions made or other actions taken by our board of directors in court. Our shareholders generally are not permitted to file a suit to reverse a decision or an action taken by our board of directors but are instead only permitted to seek damages for breaches of the duty of care and loyalty. As a matter of Swiss law, shareholder claims against a member of our board of directors for breach of the duty of care and loyalty would have to be brought in Zug, Switzerland, or where the relevant member of our board of directors is domiciled. In addition, under Swiss law, any claims by our shareholders against us must be brought exclusively in Zug, Switzerland.

Our Common Shares Are Issued Under The Laws Of Switzerland, Which May Not Protect Investors In A Similar Fashion Afforded By Incorporation In A U.S. State.

We are organized under the laws of Switzerland. However, there can be no assurance that Swiss law will not change in the future or that it will serve to protect investors in a similar fashion afforded under corporate law principles in the U.S., which could adversely affect the rights of investors.

Our Status As A Swiss Corporation May Limit Our Flexibility With Respect To Certain Aspects Of Capital Management And May Cause Us To Be Unable To Make Distributions Without Subjecting Our Shareholders To Swiss Withholding Tax.

Swiss law allows our shareholders to authorize share capital that can be issued by the board of directors without additional shareholder approval. This authorization is limited to 50% of the existing registered share capital and must be renewed by the shareholders every two years. Additionally, subject to specified exceptions, Swiss law grants preemptive rights to existing shareholders to subscribe to any new issuance of shares. Swiss law also does not provide as much flexibility in the various terms that can attach to different classes of shares as the laws of some other jurisdictions. Swiss law also reserves for approval by shareholders certain corporate actions over which a board of directors would have authority in some other jurisdictions. For example, the payment of dividends and the cancellation of treasury shares must be approved by shareholders. These Swiss law requirements relating to our capital management may limit our flexibility, and situations may arise where greater flexibility would have provided substantial benefits to our shareholders.

Under Swiss law, a Swiss corporation may pay dividends only if the corporation has sufficient distributable profits from previous fiscal years, or if the corporation has distributable reserves, each as evidenced by its audited statutory balance sheet, and after allocations to reserves required by Swiss law and our articles of association have been deducted. Freely distributable reserves are generally booked either as "free reserves" or as "capital contributions" (*Kapitaleinlagen*, contributions received from shareholders) in

the "reserve from capital contributions." Distributions may be made out of registered share capital—the aggregate par value of a company's registered shares—only by way of a capital reduction. We will not be able to pay dividends or make other distributions to shareholders on a Swiss withholding tax-free basis in excess of our aggregate qualifying contributions and registered share capital unless we increase our share capital or our reserves from capital contributions. We would also be able to pay dividends out of distributable profits or freely distributable reserves, but such dividends would be subject to Swiss withholding taxes. There can be no assurance that we will have sufficient distributable profits, free reserves, reserves from capital contributions or registered share capital to pay a dividend or effect a capital reduction, that our shareholders will approve dividends or capital reductions proposed by us or that we will be able to meet the other legal requirements for dividend payments or distributions as a result of capital reductions.

Generally, Swiss withholding tax of 35% is due on dividends and similar distributions to our shareholders, regardless of the place of residency of the shareholder, unless the distribution is made to shareholders out of (i) a reduction of registered share capital or (ii) assuming certain conditions are met, qualifying capital contribution reserves, as further described under "Taxation—Swiss Tax Considerations—Swiss Federal Withholding Tax". A U.S. holder that qualifies for benefits under the Convention between the United States of America and Switzerland for the Avoidance of Double Taxation with Respect to Taxes on Income, or the U.S.-Swiss Treaty, may apply for a refund of the tax withheld in excess of the 15% treaty rate (or in excess of the 5% reduced treaty rate for qualifying corporate shareholders with at least 10% participation in our voting shares, or for a full refund in the case of qualified pension funds). There can be no assurance that we will have sufficient qualifying capital contribution reserves to pay dividends free from Swiss withholding tax, or that Swiss withholding rules will not be changed in the future. In addition, we cannot provide assurance that the current Swiss law with respect to distributions out of qualifying capital contribution reserves will not be changed or that a change in Swiss law will not adversely affect us or our shareholders, in particular as a result of distributions out of qualifying capital contribution reserves becoming subject to additional corporate law or other restrictions. There are currently ongoing discussions in the Swiss Parliament that may limit the distribution of qualifying capital contributions. In addition, over the long term, the amount of registered share capital available to us for registered share capital reductions or qualifying capital contributions available to us to pay out as distributions is limited. If we are unable to make a distribution through a reduction in par value or out of qualifying capital contributions, we may not be able to make distributions without subjecting our shareholders to Swiss withholding taxes.

Under present Swiss tax laws, repurchases of shares for the purposes of cancellation are treated as a partial liquidation subject to 35% Swiss withholding tax on the difference between the repurchase price and the par value except, since January 1, 2011, to the extent attributable to qualifying capital contributions (*Kapitaleinlagen*) if any, the Swiss withholding becomes due. No partial liquidation treatment applies and no withholding tax is triggered if the shares are not repurchased for cancellation but held by us as treasury shares. However, should we not resell such treasury shares within six years, the withholding tax becomes due at the end of the six-year period.

Certain U.S. Shareholders May Be Subject To Adverse U.S. Federal Income Tax Consequences If We Are A Controlled Foreign Corporation.

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for United States federal income tax purposes generally is required to include in income for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of the CFC's "Subpart F income" and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. Subpart F income generally includes dividends, interest, rents and royalties, gains from the sale of securities and income from certain transactions with related parties. For tax years beginning after December 31, 2017, each Ten Percent Shareholder of a CFC is also required to include in income such Ten Percent Shareholder's share of "global intangible low-taxed income" with respect to such CFC. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in a CFC may be required to classify a portion of such gain as dividend income rather than capital gain. A non-U.S. corporation generally will be classified as a CFC for United States federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the U.S. Internal Revenue Code of 1986, as amended (the "Code")) who owns or is considered to own 10% or more of the total combined voting power of all classes of stock entitled to vote of such corporation. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. For tax years beginning after December 31, 2017, the Tax Reform Act (as defined below) expands the definition of a Ten Percent Shareholder to be a United States person (as defined by the Code) who owns or is considered to own 10% or more of the total (1) combined voting power of all classes of stock entitled to vote of such corporation or (2) value of all classes of stock of such corporation.

During our 2018 taxable year we believe that we had certain shareholders that were Ten Percent Shareholders for United States federal income tax purposes. However, our CFC status for the taxable year ended December 31, 2018 and our current taxable year is unknown and we may be a CFC for the taxable year ended December 31, 2018, our current taxable year or a following year. In addition, recent changes to the attribution rules relation to the determination of CFC status may make it difficult to determine our CFC status for any taxable year. Furthermore, because of recent changes pursuant to the Tax Cuts and Jobs Act, it is possible that our non-United States subsidiaries will be CFCs for the current taxable year or a future taxable year even if we are not a CFC for such taxable

year(s). U.S. holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a PFIC, we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Certain U.S. Shareholders May Suffer Adverse Tax Consequences If We Are Characterized As A Passive Foreign Investment Company.

Generally, if, for any taxable year, at least 75% of our gross income is passive income, or at least 50% of the value of our assets is attributable to assets that produce passive income or are held for the production of passive income, including cash, we would be characterized as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes. For purposes of these tests, passive income includes dividends, interest, and gains from the sale or exchange of investment property and rents and royalties other than rents and royalties which are received from unrelated parties in connection with the active conduct of a trade or business. If we are characterized as a PFIC, U.S. holders of our common shares may suffer adverse tax consequences, including having gains realized on the sale of the common shares treated as ordinary income, rather than capital gain, the loss of the preferential rate applicable to dividends received on the common shares by individuals who are U.S. holders, and having interest charges apply to distributions by us and the proceeds of sales of the common shares.

Our status as a PFIC will depend on the composition of our income and the composition and value of our assets which may be determined in part by reference to the quarterly market value of our common shares, which may be volatile. Our status may also depend, in part, on how, and how quickly, we utilize the cash proceeds from prior offerings in our business. Our status as a PFIC is a fact-intensive determination made on an annual basis and we cannot provide any assurances regarding our PFIC status for any past, current or future taxable years.

Because it is possible we were a PFIC for the 2017 taxable year, we provided information necessary for our shareholders to make a QEF election with respect to us for the 2017 taxable year. We provided such information on our website (www.crisprtx.com). For the 2017 taxable year, the amount of our ordinary earnings and net capital gain for purposes of the QEF inclusion rules was zero. Although we have not yet determined whether we are a PFIC for the 2018 taxable year, it is possible that we may be a PFIC for the 2018 year as well. We will endeavor to provide to you, for each taxable year that we determine we are or may be a PFIC, a PFIC Annual Information Statement containing information necessary for you to make a QEF election with respect to us.

If we are determined to be a PFIC, a U.S. holder will generally be treated as owning a proportionate amount (by value) of shares owned by us in any of our direct or indirect subsidiaries that are also PFICs, each a lower-tier PFIC, and will be subject to similar adverse rules with respect to distributions from, or dispositions of, such lower-tier PFICs, in each case as if such U.S. holder held such shares directly (even if such U.S. holder does not receive the proceeds of such distributions or dispositions directly). We have not determined whether any of our subsidiaries (including TRACR Hematology Ltd. and CRISPR Therapeutics Ltd.) are or may be lower-tier PFICs for any prior taxable year, the current taxable year or future taxable years, and we do not intend to do so. We also do not intend to make available the information necessary for U.S. holders to make a QEF election with respect to any lower-tier PFICs and therefore you should expect that you will not be able to make a QEF election with respect to them. Because of recent changes pursuant to the Tax Cuts and Jobs Act, which may cause our non-United States subsidiaries to be treated as CFCs, even if we are not treated as a CFC, it is possible that our non-United States subsidiaries are also PFICs. You are urged to consult your own tax advisors regarding our PFIC status and the tax considerations relevant to an investment in a PFIC, including the availability, and advisability, of, and procedure for making, a QEF election with respect to us, and the application of the PFIC rules to any of our subsidiaries.

U.S. Shareholders May Not Be Able To Obtain Judgments Or Enforce Civil Liabilities Against Us Or Our Executive Officers Or Members Of Our Board Of Directors.

We are organized under the laws of Switzerland and our registered office and domicile is located in Zug, Switzerland. Moreover, certain of our directors and executive officers and a number of directors of each of our subsidiaries are not residents of the United States, and all or a substantial portion of the assets of such persons are located outside the United States. As a result, it may not be possible for investors to effect service of process within the United States upon us or upon such persons or to enforce against them judgments obtained in U.S. courts, including judgments in actions predicated upon the civil liability provisions of the federal securities laws of the United States. We have been advised by our Swiss counsel that there is doubt as to the enforceability in Switzerland of original actions, or in actions for enforcement of judgments of U.S. courts, of civil liabilities to the extent solely predicated upon the federal and state securities laws of the United States. Original actions against persons in Switzerland based solely upon the U.S. federal or state securities laws are governed, among other things, by the principles set forth in the Swiss Federal Act on Private International Law. This statute provides that the application of provisions of non-Swiss law by the courts in Switzerland shall be precluded if the result is incompatible with Swiss public policy. Also, mandatory provisions of Swiss law may be applicable regardless of any other law that would otherwise apply.

Switzerland and the United States do not have a treaty providing for reciprocal recognition and enforcement of judgments in civil and commercial matters. The recognition and enforcement of a judgment of the courts of the United States in Switzerland is governed by the principles set forth in the Swiss Federal Act on Private International Law. This statute provides in principle that a judgment rendered by a non-Swiss court may be enforced in Switzerland only if:

- the non-Swiss court had jurisdiction pursuant to the Swiss Federal Act on Private International Law;
- the judgment of such non-Swiss court has become final and non-appealable;
- the judgment does not contravene Swiss public policy;
- the court procedures and the service of documents leading to the judgment were in accordance with the due process of law; and
- no proceeding involving the same position and the same subject matter was first brought in Switzerland, or adjudicated in Switzerland, or was earlier adjudicated in a third state and this decision is recognizable in Switzerland.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal executive offices are located in Zug, Switzerland pursuant to a real estate lease agreement with a term that renews every three months. We also have facilities in Cambridge, Massachusetts, where we occupy approximately 65,376 square feet of laboratory and office space under a sublease that expires in December 2026, which includes an option to extend the lease for five years. We also lease approximately 19,817 square feet of additional office and laboratory space in Cambridge, Massachusetts pursuant to a lease that expires in February 2022. We believe that our facilities are adequate for our current needs and that suitable additional or substitute space would be available if needed.

Item 3. Legal Proceedings.

From time to time, we may become involved in litigation or other legal proceedings relating to claims arising from the ordinary course of business. There are currently no claims or actions pending against us that, in the opinion of our management, are likely to have a material adverse effect on our business.

In January 2016, the U.S. Patent and Trademark Office, or USPTO, declared an interference between one of the pending U.S. patent applications we have in-licensed from Dr. Charpentier and twelve issued U.S. patents owned jointly by the Broad Institute and Massachusetts Institute of Technology and, in some instances, the President and Fellows of Harvard College, which we refer to individually and collectively as Broad. The interference was redeclared in March 2016 to add a U.S. patent application owned by Broad. An interference is a proceeding conducted at the USPTO by the Patent Trial and Appeal Board, or PTAB, to determine which party was the first to invent subject matter claimed by at least two parties. There were two parties to this interference being Dr. Charpentier, the Regents of the University of California, and the University of Vienna (collectively, "CVC") and Broad.

Following motions by the parties and other procedural matters, in February 2017, the PTAB concluded that the declared interference should be dismissed. In its decision, the PTAB concluded that, although the claims overlap, the respective scope of CVC's and Broad's claim sets as presented did not define the same patentable invention and, accordingly, terminated the interference.

In April 2017, CVC appealed the PTAB decision to the U.S. Court of Appeals for the Federal Circuit, or the Federal Circuit. In the appeal, CVC asked the court to review and reverse the PTAB's February 2017 decision, which terminated the interference without determining which inventors actually invented the use of the CRISPR/Cas9 genome editing technology in eukaryotic cells. The Federal Circuit conducted a hearing on the appeal on April 30, 2018. On September 10, 2018, the Federal Circuit affirmed the PTAB's decision to terminate the interference proceeding.

Either party can pursue existing or new patent applications in the U.S. and elsewhere. Going forward, either party and other parties could seek a new interference related to the uses of the technology in eukaryotic cells or other aspects of the technology, and any existing or new patents could be the subject of other challenges to their validity of enforceability. If there is a second interference, either party could again appeal an adverse decision to the Federal Circuit.

In any case, it may be years before there is a final determination on priority. Pursuant to the terms of the license agreement with Dr. Charpentier, we are responsible for covering or reimbursing Dr. Charpentier's patent prosecution, defense and related costs associated with our in-licensed technology.

In February 2018, several parties filed oppositions in the European Patent Office to the grant of our first in-licensed European patent. Later in 2018, several parties filed oppositions in the European Patent Office to the grant of our second in-licensed European patent. Opposition proceedings can lead to the revocation of a patent in its entirety; the maintenance of the patent as granted, or the maintenance of a patent in amended form. Opposition proceedings typically take years to resolve, including the time taken by appeals that can be filed by any of the parties. We cannot guarantee the outcome of the oppositions to our in-licensed European patent, and an adverse result could preclude us from enforcing our rights in Europe against third parties.

We are unable to predict the outcome of these matters and are unable to make a meaningful estimate of the amount or range of loss, if any, that could result from an unfavorable outcome. In the future, we may become party to legal matters and claims arising in the ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our financial position, results of operations or cash flows. We devote considerable effort in building, maintaining and protecting a broad, worldwide estate of intellectual property related to the use of CRISPR/Cas9 genome editing systems to develop therapeutic products. In this regard, we have amassed an estate of patents, patent applications and other intellectual property covering, among other things:

- fundamental aspects of CRISPR/Cas9 systems for gene editing via the in-licensed patent rights of Dr. Emmanuelle Charpentier;
- internally developed platform technologies supporting the use of CRISPR/Cas9 genome editing systems;
- guide RNAs directed to specific targets as treatments for specific diseases;
- improved delivery technologies; and
- all aspects of our specific development candidates.

As both our platform and development pipeline mature, we intend to continue expanding our intellectual property portfolio through new patent filings that claim aspects of our proprietary technologies and development candidates. Furthermore, as the field of CRISPR/Cas9 technologies and therapeutics is maturing, patent applications are being examined by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom and with what claims.

It is likely that there will be significant litigation and other proceedings, such as interference, reexamination, inter partes review, post-grant review and opposition proceedings, in various patent offices relating to patent rights in the CRISPR/Cas9 field. For example, the European patents we in-licensed from Dr. Charpentier have been opposed by several third parties. On September 16, 2012, the America Invents Act went into effect and expanded the opportunities to challenge issued U.S. patents, creating proceedings including inter partes reviews and post-grant reviews. These provide additional opportunities for third parties to challenge patents within our intellectual property estate. Given the importance of our intellectual property estate to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area, as we deem appropriate.

For further information regarding risks regarding the interference and patent rights held by third parties, please see "Risk Factors—Risks Related to Our Intellectual Property" contained in Item 1A of this report.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

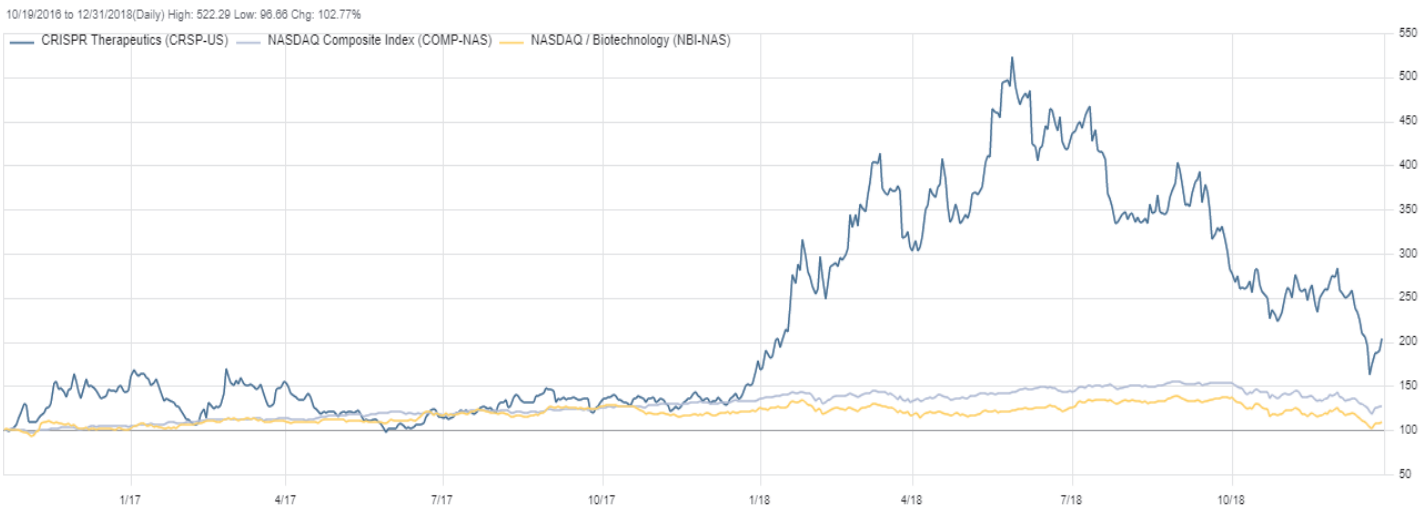
Our common stock is traded on The Nasdaq Global Market under the symbol "CRSP."

Stock Performance Graph

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

The graph set forth below compares the cumulative total stockholder return on our shares between October 19, 2016 (the date of our initial public offering) and December 31, 2018, with the cumulative total return of (a) the Nasdaq Biotechnology Index and (b) the Nasdaq Composite Index, over the same period. This graph assumes the investment of $100 on October 19, 2016 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The graph assumes our closing sales price on October 19, 2016 of $14.09 per share as the initial value of our common shares and not the initial offering price to the public of $14.00 per share. The comparisons shown in the graph below are based upon historical data. The stock price performance included in this graph is not necessarily indicative of future stock price performance.

Comparison of Total Return Among CRISPR Therapeutics AG, the NASDAQ Composite Index and the NASDAQ Biotechnology Index



Holders

As of February 21, 2019, we had approximately 11 holders of record of our common shares. This number does not include beneficial owners whose shares were held in street name.

Dividends

We have not paid any cash dividends on our common shares since inception and do not anticipate paying cash dividends in the foreseeable future.

Securities authorized for issuance under equity compensation plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

Purchase of Equity Securities

In the third quarter of 2018, the Company repurchased 64,211 shares of restricted common stock from former employees for less than $0.1 million

Item 6. Selected Financial Data.

SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data are derived from our audited consolidated financial statements. These data should be read in conjunction with our audited consolidated financial statements and related notes that are included elsewhere in this Annual Report on Form 10-K and with "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in Item 7.

	December 31,				
	2018	2017	2016	2015	2014
	(in thousands, except share and per share amounts)				
Consolidated Statements of Operations Data:					
Collaboration revenue	$ 3,124	$ 40,997	$ 5,164	$ 247	$ —
Operating expenses:					
Research and development	113,773	69,800	42,238	12,573	1,513
General and administrative	48,294	35,845	31,056	13,403	5,114
Total operating expenses	162,067	105,645	73,294	25,976	6,627
Loss from operations	(158,943)	(64,648)	(68,130)	(25,729)	(6,627)
Other (expense) income, net	(5,485)	(1,960)	45,412	(92)	(236)
Net loss before (provision for) benefit from income taxes	(164,428)	(66,608)	(22,718)	(25,821)	(6,863)
(Provision for) benefit from income taxes	(553)	(1,749)	(484)	(7)	63
Net loss	(164,981)	(68,357)	(23,202)	(25,828)	(6,800)
Foreign currency translation adjustment	(22)	40	(18)	(6)	(2)
Comprehensive loss	$ (165,003)	(68,317)	$ (23,220)	$ (25,834)	$ (6,802)
Reconciliation of net loss to net loss attributable to common shareholders:					
Net loss	$ (164,981)	$ (68,357)	$ (23,220)	$ (25,828)	$ (6,800)
Loss attributable to noncontrolling interest	—	—	25	325	536
Loss on extinguishment of redeemable convertible preferred shares	—	—	—	—	(745)
Net loss attributable to common shareholders	$ (164,981)	$ (68,357)	$ (23,177)	$ (25,503)	$ (7,009)
Net loss per share attributable to common shareholders, basic and diluted	$ (3.44)	$ (1.71)	$ (1.89)	$ (5.06)	$ (1.97)
Weighted-average common shares outstanding, basic and diluted	47,964,368	40,057,365	12,257,483	5,037,404	3,559,985

	December 31,				
	2018	2017	2016	2015	2014
	(in thousands)				
Consolidated Balance Sheet Data:					
Cash	$ 456,649	$ 239,758	$ 315,520	$ 155,961	$ 945
Working capital	438,649	233,874	298,190	146,685	(1,178)
Total assets	489,016	271,346	344,962	159,423	1,527
Redeemable convertible preferred shares	—	—	—	64,521	6,270
Total shareholders' equity (deficit)	392,195	187,832	232,846	(29,124)	(6,974)

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

You should read the following discussion and analysis of our financial condition and results of operations together with the section entitled "Selected Consolidated Financial Data" and our consolidated financial statements and related notes appearing 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 and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report 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.

Investors and others should note that we announce material information to our investors using our investor relations website (https://crisprtx.gcs-web.com/), SEC filings, press releases, public conference calls and webcasts. We use these channels as well as social media to communicate with the public about our company, our business, our product candidates and other matters. It is possible that the information we post on social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the social media channels listed on our investor relations website.

Overview

We are a leading gene editing company focused on the development of CRISPR/Cas9-based therapeutics. CRISPR/Cas9 is a revolutionary gene editing technology that allows for precise, directed changes to genomic DNA. The application of CRISPR/Cas9 for gene editing was co-invented by one of our scientific founders, Dr. Emmanuelle Charpentier, who, along with her collaborators, published work elucidating how CRISPR/Cas9, a naturally occurring viral defense mechanism found in bacteria, can be adapted for use in gene editing. We are applying this technology to potentially treat a broad set of rare and common diseases by disrupting, correcting or regulating the genes related to the disease. We believe that our scientific expertise, together with our approach, may enable an entirely new class of highly active and potentially curative therapies for patients for whom current biopharmaceutical approaches have had limited success.

Since our inception in October 2013, we have devoted substantially all of our resources to our research and development efforts, identifying potential product candidates, undertaking drug discovery and preclinical development activities, building and protecting our intellectual property estate, organizing and staffing our company, business planning, raising capital, and providing general and administrative support for these operations. To date, we have primarily financed our operations through private placements of our preferred shares, common stock issuances, convertible loans and collaboration agreements with strategic partners.

In January 2018, we completed an offering of 5,750,000 of our common shares, which were sold at a price of $22.75 per share. This offering resulted in net proceeds of $122.6 million. The underwriting discount of $7.8 million and other expenses of $0.4 million related to the equity offering were recorded as an offset to additional paid-in capital. In September 2018, we completed an offering of 4,210,526 common shares, which were sold at a price to the public of $47.50 per share. This offering resulted in net proceeds of $187.6 million. The underwriting discount of $12.0 million and other expenses of $0.4 million related to the equity offering were recorded as an offset to additional paid-in capital. In addition, $3.1 million of stamp taxes on the issuance proceeds from the January and September offerings were recorded as an offset to additional paid in capital.

In addition, in August 2018, we entered into an At-The-Market ("ATM") sales agreement with Jefferies LLC ("Jefferies"), under which we may offer and sell from time to time common shares having aggregate gross proceeds of up to $125.0 million. We have not yet issued or sold any securities under this sales agreement.

All of our revenue to date has been collaboration revenue. We have incurred significant net operating losses in every year since our inception and expect to continue to incur net operating losses for the foreseeable future. As of December 31, 2018, we had $456.6 million in cash and an accumulated deficit of $291.6 million. We expect to continue to incur significant expenses and increasing operating losses for the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase significantly as we continue our current research programs and development activities; seek to identify additional research programs and additional product candidates, conduct initial drug application supporting preclinical studies and initiate clinical trials for our product candidates; initiate preclinical testing and clinical trials for any other product candidates we identify and develop, maintain, expand and protect our intellectual property estate, further develop our gene editing platform; hire additional research, clinical and scientific personnel; and incur additional costs associated with operating as a public company.

Collaboration Agreement, Joint Development and Commercialization Agreement- Vertex

In October 2015, we entered into a strategic research collaboration agreement with Vertex focused on the development of CRISPR/Cas9-based therapies. Under the terms of our agreement, we received an upfront, nonrefundable payment of $75.0 million and $30.0 million in convertible loan proceeds.

In December 2017, we and Vertex entered into an amendment to the collaboration agreement ("Amendment"). The Amendment, among other things, modified certain definitions and provisions of the Collaboration Agreement to make them consistent with the Joint Development Agreement ("JDA") and clarified how many options are exercised (or deemed exercised) in connection with certain targets specified under the collaboration agreement. The Amendment also amended other provisions of the collaboration agreement, including the expiration terms of the collaboration agreement.

In December 2017, we entered into the JDA with Vertex for the development and commercialization of CTX001. The initial focus of the JDA centers on developing CTX001 for beta thalassemia and SCD. CTX001 is an investigational autologous gene-edited hematopoietic stem cell therapy for patients suffering from severe hemoglobinopathies. The net profits and net losses, as applicable, incurred under the JDA will be shared equally between us and Vertex.

We and Vertex are planning to conduct clinical trials for CTX001 in multiple countries for both beta thalassemia and severe sickle cell disease (SCD) trials and we and Vertex continue to work closely with various global regulatory authorities in these and other countries.

We and Vertex are investigating CTX001 in a Phase 1/2 open-label clinical trial designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with TDT, non-beta zero/beta zero subtypes. The first two patients in the trial will be treated sequentially and, pending data from these initial two patients, the trial will open for broader concurrent enrollment. The first patient has been treated with CTX001 in this trial. The study is currently being conducted at multiple clinical trial sites in Canada and Europe. In addition, CRISPR Therapeutics and Vertex plan to expand this trial to include sites in the United States.

We and Vertex are also investigating CTX001 in a Phase 1/2 open-label clinical trial designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with severe SCD. In April 2018, we and Vertex submitted an Investigational New Drug application ("IND") for CTX001 to the U.S. Food and Drug Administration (the "FDA") to support the planned initiation of a Phase 1/2 trial in the U.S. in adult patients with SCD. In May 2018, the FDA placed a clinical hold on the IND for CTX001 for the treatment of SCD pending the resolution of certain questions as part of its review of the IND. On October 10, 2018, we and Vertex announced that the FDA has lifted the clinical hold and accepted the IND for CTX001 for the treatment of sickle cell disease. In addition, we and Vertex have obtained approvals of Clinical Trial Applications (CTAs) for CTX001 for SCD in Canada and additional countries in Europe. Similar to the trial in beta thalassemia, the first two patients in this trial will be treated sequentially prior to broader concurrent enrollment and, pending data from these initial two patients, the trial will open for broader concurrent enrollment. The trial is currently being conducted at clinical trial sites in the United States and the first patient in this trial has been enrolled. CTX001 was granted Fast Track Designation by the U.S. Food and Drug Administration for the treatment of SCD.

Joint Venture Agreement- Casebia

In December 2015, we entered into an agreement, (the "JV Agreement"), with Bayer to create a joint venture, Casebia Therapeutics LLP, ("Casebia" or the "JV"), to discover, develop and commercialize CRISPR/Cas9 gene-editing therapeutics to treat the genetic causes of bleeding disorders, autoimmune disease, blindness, hearing loss and heart disease. We and Bayer each have a 50% interest in the JV. Under the JV Agreement, Bayer is making available its protein engineering expertise and relevant disease know-how and we are contributing our proprietary CRISPR/Cas9 gene editing technology and intellectual property. Bayer will also provide up to $300.0 million in research and development investments to the JV over the first five years, subject to specified conditions.

In connection with the JV Agreement, the JV was required to pay us an aggregate amount of $35.0 million technology access fee, consisting of an upfront payment of $20.0 million, which was paid at the closing of the JV Agreement in March 2016, and another payment of $15.0 million for specified intellectual property rights relating to our gene-editing technology outside of the United States, which was paid in December 2016. In January 2016, we also issued the Bayer Convertible Loan to Bayer BV for gross proceeds of $35.0 million which was immediately converted to Series B Preferred Shares at a conversion price of $13.43 per share. Concurrent with our initial public offering in October 2016, we issued and sold 2,500,000 common shares to Bayer BV, at the public offering price of $14.00 per share resulting in aggregate net proceeds of $35.0 million.

Collaboration Agreement- ViaCyte

On September 17, 2018, we entered into a research collaboration agreement ("ViaCyte Collaboration Agreement") with ViaCyte, Inc. (“ViaCyte”) focused on the discovery, development, and commercialization of gene-edited allogeneic stem cell therapies for the treatment of diabetes. Under the terms of the ViaCyte Collaboration Agreement, we and ViaCyte will jointly seek to develop an immune-evasive stem cell line as a first step on the path to an allogeneic stem-cell derived product. Upon successful completion of these studies and identification of a product candidate, we and ViaCyte will jointly assume responsibility for further development and commercialization worldwide.

Upon execution of the agreement, ViaCyte was entitled to receive $15.0 million from us that was owed in two installments, payable either in cash or in common shares at the Company’s option. The agreement included certain provisions such that in the event ViaCyte sold shares received from us for less than $15.0 million in combined net proceeds, we would owe ViaCyte the deficient amount. In the event ViaCyte sold shares received from us for greater than $15.0 million in combined net proceeds, ViaCyte would owe us the surplus amount. On September 24, 2018, we issued 165,636 common shares to ViaCyte which had a fair value of $7.5 million. These shares were subsequently sold for $6.9 million, resulting in a deficient amount of $0.6 million. On November 15, 2018, we issued 214,512 common shares to ViaCyte, which had a fair value of $8.1 million. These shares were subsequently sold for $7.5 million, resulting in a deficient amount of $0.6 million, which was paid in cash on December 18, 2018.

At the time of the agreement, ViaCyte had the option, under certain circumstances, to receive an additional $10.0 million from us in the form of a convertible promissory note at fair value. As of November 2018, these circumstances no longer provide ViaCyte with that option. The ViaCyte Collaboration Agreement may remain in force for up to six years.

Financial Overview

Revenue Recognition

We have not generated any revenue to date from product sales and do not expect to do so in the near future. During the years ended December 31, 2018, 2017 and 2016 we recognized $3.1 million, $41.0 million and $5.2 million, respectively, of revenue related to our collaboration agreements with Vertex and Casebia. As of December 31, 2018, we had not received any milestone or royalty payments under the Vertex collaboration agreement. For additional information about our revenue recognition policy, see the “Critical Accounting Policies and Estimates—*Revenue*.”

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our product discovery efforts and the development of our product candidates, which include:

- employee-related expenses, including salaries, benefits and equity-based compensation expense;
- costs of services performed by third parties that conduct research and development and preclinical activities on our behalf;
- costs of purchasing lab supplies and non-capital equipment used in our preclinical activities and in manufacturing preclinical study materials;
- consultant fees;
- facility costs, including rent, depreciation and maintenance expenses; and
- fees and other payments related to acquiring and maintaining licenses under our third-party licensing agreements.

Research and development costs are expensed as incurred. Nonrefundable advance payments for research and development goods or services to be received in the future are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed. At this time, we cannot reasonably estimate or know the nature, timing or estimated costs of the efforts that will be necessary to complete the development of any product candidates we may identify and develop. This is due to the numerous risks and uncertainties associated with developing such product candidates, including the uncertainty of:

- successful completion of preclinical studies and Investigational New Drug-enabling studies;
- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;

- obtaining and maintaining patent and trade secret protection and non-patent exclusivity;
- launching commercial sales of the product, if and when approved, whether alone or in collaboration with others;
- acceptance of the product, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies and treatment options;
- a continued acceptable safety profile following approval;
- enforcing and defending intellectual property and proprietary rights and claims; and
- achieving desirable medicinal properties for the intended indications.

A change in the outcome of any of these variables with respect to the development of any product candidates we may develop could significantly change the costs, timing and viability associated with the development of that product candidate.

Except for activities we perform in connection with our collaborations with Vertex and Casebia, we do not track research and development costs on a program-by-program basis.

Research and development activities are central to our business model. We expect research and development costs to increase significantly for the foreseeable future as our current development programs progress and new programs are added.

General and Administrative Expenses

General and administrative expenses consist primarily of employee related expenses, including salaries, benefits, and equity-based compensation, for personnel in executive, finance, accounting, business development and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters, and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will increase in the future to support continued research and development activities, potential commercialization of our product candidates and increased costs of operating as a public company. We anticipate increased costs associated with being a public company, including expenses related to services associated with maintaining compliance with exchange listing and SEC requirements, insurance costs and investor relations costs, the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses. We also anticipate increased expenses related to the reimbursements of third-party patent related expenses in connection with the ongoing interference proceeding with respect to certain of our in-licensed intellectual property.

Results of Operations

Comparison of Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017, together with the dollar change in those items:

	Years Ended December 31,		Period-to-Period Change
	2018	2017	
		(in thousands)	
Collaboration revenue	$ 3,124	$ 40,997	$ (37,873)
Operating expenses:			
Research and development	113,773	69,800	43,973
General and administrative	48,294	35,845	12,449
Total operating expenses	162,067	105,645	56,422
Loss from operations	(158,943)	(64,648)	(94,295)
Other expense, net	(5,485)	(1,960)	(3,525)
Net loss before provision for from income taxes	(164,428)	(66,608)	(97,820)
Provision for income taxes	(553)	(1,749)	1,196
Net loss	$ (164,981)	$ (68,357)	$ (96,624)

Collaboration Revenue

Collaboration revenue for the year ended December 31, 2018 was $3.1 million, compared to $41.0 million for the year ended December 31, 2017. The decrease of $37.9 million was primarily due to recognition of $30.3 million in revenue in 2017 as a result of the delivery of the co-exclusive licenses to develop and commercialize various hemoglobinopathy targets under the collaboration agreement with Vertex as well as a decrease in research and development service revenue from the collaboration with Vertex.

Research and Development Expenses

Research and development expenses for the year ended December 31, 2018 was $113.8 million, compared to $69.8 million for the year ended December 31, 2017. The increase of $44.0 million was primarily attributable to the following increases: $15.0 million of expenses related to the ViaCyte Collaboration Agreement, $7.5 million of variable research and development costs and license fees, $8.8 million of stock-based compensation costs, $9.5 million of employee-related costs, and $2.5 million of facility-related costs.

General and Administrative Expenses

General and administrative expenses were $48.3 million for the year ended December 31, 2018, compared to $35.8 million for the year ended December 31, 2017. The increase of $12.5 million was primarily due to the following increases: $7.4 million of stock-based compensation costs, $3.5 million in intellectual property costs and $2.8 million in employee-related costs. The increases were offset by a reduction of $1.2 million in professional, consulting and facilities costs.

Other (expense) income

Other expense, net, was $5.5 million for the year ended December 31, 2018, compared to $2.0 million for the year ended December 31, 2017. The increase was primarily due to an increase in the loss from equity method investment from stock-based compensation awards granted to employees of Casebia of $2.5 million and other expenses of $1.2 million related to the change in fair value of the derivative liability issued under the ViaCyte Collaboration Agreement. The increases were offset by $0.2 million of investment income for the year ended December 31, 2018.

Comparison of Years Ended December 31, 2017, and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016, together with the dollar change in those items:

	Years Ended December 31,		Period-to-Period Change
	2017	2016	
		(in thousands)	
Collaboration revenue	40,997	5,164	$ 35,833
Operating expenses:			
Research and development	69,800	42,238	27,562
General and administrative	35,845	31,056	4,789
Total operating expenses	105,645	73,294	32,351
Loss from operations	(64,648)	(68,130)	3,482
Other (expense) income, net	(1,960)	45,412	(47,372)
Net loss before provision for income taxes	(66,608)	(22,718)	(43,890)
Provision for income taxes	(1,749)	(484)	(1,265)
Net loss	$ (68,357)	$ (23,202)	$ (45,155)

Collaboration Revenue

Collaboration revenue for the year ended December 31, 2017 was $41.0 million, compared to $5.2 million for the year ended December 31, 2016. The increase of $35.8 million was primarily due to $30.3 million of revenue recognized in conjunction with the delivery of co-exclusive licenses to develop and commercialize various hemoglobinopathy targets under the Collaboration Agreement with Vertex and in connection with the execution of the JDA with Vertex, an increase in research and development service revenue from the collaboration with Vertex of $32.2 million, and an increase in research and development service revenue of $3.6 million from a collaboration agreement with Casebia. During the year ended December 31, 2016, we recognized $4.0 million and $1.2 million of research and development service revenue related to the collaboration with Vertex and Casebia, respectively.

Research and Development Expenses

Research and development expenses for the year ended December 31, 2017 was $69.8 million, compared to $42.2 million for the year ended December 31, 2016. The increase of $27.6 million in research and development expenses was primarily attributable to approximately $3.9 million in increased facilities costs including rent and utilities, $11.1 million in increased research and development variable process and platform development costs, $8.5 million in increased research and development employee compensation costs, $4.0 million in increased stock-based compensation costs and $0.1 million in increased consulting and professional services.

General and Administrative Expenses

General and administrative expenses were $35.8 million for the year ended December 31, 2017, compared to $31.1 million for the year ended December 31, 2016. The increase of $4.8 million was primarily due to the following increases in expenses: $3.7 million of employee-related costs to support our overall growth and $2.7 million in facilities costs including rent and utilities, partially offset by a decreases of $1.6 million of intellectual property costs including related to prior year third-party costs to procure the issuance of patents in jurisdictions outside the United States and costs related to an interference proceeding with respect to our in-licensed intellectual property.

Other Income (Expense), Net

Other (expense) income, net, was $2.0 million of expense for the year ended December 31, 2017, compared to $45.4 million of income for the year ended December 31, 2016. The decrease of $47.4 million was primarily due to a loss from the equity method investment of $1.8 million as a result of stock based compensation awards with Casebia employees and other expenses of $0.2 million during 2017 as compared to a $78.5 million gain recognized in connection with the formation of Casebia which equaled the value of cash consideration received from Casebia and the fair value of the Company's equity interest in Casebia as of the formation of the JV in 2016, combined with an $11.5 million gain recognized on extinguishment of convertible loans with Vertex, all of which was partially offset by $36.5 million in 2016 equity method losses, and $8.1 million of interest expense related to a convertible loan with Bayer.

Liquidity and Capital Resources

As of December 31, 2018, we had cash and cash equivalents of approximately $456.6 million, of which $447.5 million was held outside of the United States. In January 2018, we completed an offering of 5,750,000 of our common shares, which were sold at a price of $22.75 per share. This offering resulted in net proceeds of $122.6 million. The underwriting discount of $7.8 million and other expenses of $0.4 million related to the equity offering were recorded as an offset to additional paid-in capital. In September 2018, we completed an offering of 4,210,526 common shares, which were sold at a price to the public of $47.50 per share. This offering resulted in net proceeds of $187.6 million. The underwriting discount of $12.0 million and other expenses of $0.4 million related to the equity offering were recorded as an offset to additional paid-in capital. In addition, $3.1 million of stamp taxes on the issuance proceeds from the January and September offerings were recorded as an offset to additional paid in capital. With our cash on hand as of December 31, 2018, we expect cash and cash equivalents to be sufficient to fund its current operating plan through at least the next 24 months.

In addition, in August 2018, we entered into an At-The-Market ("ATM") sales agreement with Jefferies LLC ("Jefferies"), under which we may offer and sell from time to time common shares having aggregate gross proceeds of up to $125.0 million. We have not yet issued or sold any securities under this sales agreement.

We have incurred losses and cumulative negative cash flows from operations since our inception, and as of December 31, 2018, we had an accumulated deficit of $291.6 million. We anticipate that we will continue to incur losses for at least the next several years. We expect that our research and development and general and administrative expenses will continue to increase and, as a result, we will need additional capital to fund our operations, which we may raise through public or private equity or debt financings, strategic collaborations, or other sources.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, research and development activities, compensation and related expenses, laboratory and related supplies, legal and other regulatory expenses, patent prosecution filing and maintenance costs for our licensed intellectual property and general overhead costs. We expect our expenses to increase compared to prior periods in connection with our ongoing activities, particularly as we continue research and development and preclinical activities, initiate preclinical studies to support initial drug applications. In addition, we expect to incur additional costs associated with operating as a public company.

Because our research programs are still in early stages of 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 current or future product candidates, if approved, 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 cash needs through a combination of equity, debt financings and payments received in connection with our collaboration agreements. We are entitled to research payments under our collaboration with Vertex. Additionally, we are eligible to earn payments, in each case, on a per-product basis under the JV Agreement with Bayer for Casebia and our collaboration with Vertex. Except for these sources of funding, we do not have any committed external source of liquidity. We intend to consider opportunities to raise additional funds through the sale of equity or debt securities when market conditions are favorable to us to do so. To the extent that we raise additional capital through the future sale of equity or debt securities, the ownership interests of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing shareholders. 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 or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Outlook

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect our existing cash, will enable us to fund our operating expenses and capital expenditures for at least the next 24 months, without giving effect to any additional proceeds we may receive under our Collaboration Agreement and JDA with Vertex and the agreements related to Casebia and any other capital raising transactions we may complete. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Given our need for additional financing to support the long term clinical development of our programs, we intend to consider additional financing opportunities when market terms are favorable to us.

Our ability to generate revenue and achieve profitability depends significantly on our success in many areas, including: developing our delivery technologies and our gene-editing 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, if approved; 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 estate of intellectual property rights, including patents, trade secrets and know-how; and attracting, hiring and retaining qualified personnel

Sources of Liquidity

Cash Flows

The following table provides information regarding our cash flows for each of the periods below:

	Years Ended December 31,		
	2018	2017	2016
	(in thousands)		
Net cash used in operating activities	$ (96,239)	$ (70,093)	$ (52,860)
Net cash (used in) provided by investing activities	(2,773)	(8,314)	31,884
Net cash provided by financing activities	315,934	2,608	183,220
Effect of exchange rate changes on cash	(22)	41	(235)
Increase (decrease) in cash and restricted cash	$ 216,900	$ (75,758)	$ 162,009

Net Cash (Used in) Provided by Operating Activities

Net cash used in operating activities was $96.2 million for the year ended December 31, 2018 and primarily consisted of a net loss of $165.0 million adjusted for non-cash items (including equity-based compensation expense of $35.0 million, depreciation and amortization expense of $3.5 million and a loss from equity method investment of $4.3 million), a decrease in prepaid expenses and other current assets of $3.3 million, an increase in accounts payable and accrued expenses of $12.1 million, an increase in deferred revenue of $0.3 million and a decrease in deferred rent of $0.7 million, partially offset by a decrease of $2.5 million in accounts receivable and a decrease in other liabilities of $0.2 million.

Net cash used in operating activities was $70.1 million for the year ended December 31, 2017 and primarily consisted of a net loss of $68.4 million adjusted for non-cash items (including equity-based compensation expense of $18.9 million, depreciation and amortization expense of $3.0 million and a loss from equity method investment of $1.8 million), an increase in prepaid expenses and other current assets of $4.1 million, a decrease in accounts payable and accrued expenses of $0.8 million, a decrease in deferred revenue of $20.7 million and a decrease in deferred rent of $0.5 million, partially offset by a decrease of $0.5 million in accounts receivable and an increase in other liabilities of $0.3 million.

Net cash used in operating activities was $52.9 million for the year ended December 31, 2016 and primarily consisted of a net loss of $23.2 million adjusted for non-cash items (including equity-based compensation expense of $10.8 million, non-cash interest expense of $8.1 million, depreciation and amortization expense of $0.9 million, loss from equity method investment of $36.4 million, other income of $78.6 million recognized in connection with the formation of our JV with Bayer HealthCare, and a gain on extinguishment of the Vertex convertible loan of $11.5 million), an increase in prepaid expenses and other current assets of $1.1 million, and an increase in accounts receivable of $2.8 million, partially offset by an increase in accounts payable and accrued expenses of $3.9 million, deferred revenue of $1.9 million, and deferred rent of $2.4 million.

Net Cash (Used in) Provided by Investing Activities

Net cash used in investing activities for the year ended December 31, 2018 was $2.8 million and consisted of purchases of property and equipment for use in research and development activities.

Net cash used in investing activities for the year ended December 31, 2017 was $8.3 million and consisted primarily of purchases of property and equipment for use in research and development activities and leasehold improvements for our Cambridge, MA office.

Net cash provided by investing activities for the year ended December 31, 2016 was $31.9 million and consisted primarily of consisted of proceeds of $35.0 million from our contribution of intellectual property to the JV, offset by our contributions to the JV of $0.1 million, and the purchase of property and equipment of $3.0 million primarily associated with the commencement of internal research and development.

Net Cash Provided by Financing Activities

Net Cash provided by financing activities for the year ended December 31, 2018 was $315.9 million and consisted of net proceeds of $307.1 million from the issuance of common shares and net proceeds of $8.9 million from stock option exercises, offset by $0.1 million for the repurchase of common shares.

Net Cash provided by financing activities for the year ended December 31, 2017 was $2.6 million and consisted entirely of net proceeds from stock option exercises.

Net Cash provided by financing activities for the year ended December 31, 2016 was $183.2 million and consisted of net proceeds of $54.1 million from the issuance of common shares in the IPO, proceeds of $35.0 million from the issuance of common shares in a private placement with Bayer, gross proceeds of $22.9 million from the issuance of Series A-3 preferred shares, gross proceeds of $38.1 million from the issuance of Series B preferred shares and $35.0 million in proceeds from the issuance of a convertible loan to Bayer, offset by the issuance costs on preferred share financings of $1.8 million.

Contractual Obligations

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2018 (in thousands):

	Year 1	Year 2-3	More than 3 Years	Total
Operating lease and sublease commitments	$ 6,275	$ 13,938	$ 30,368	$ 50,581

The amounts above are net of payment to be received under a sublease agreement, totaling $0.4 million in 2019.

We enter into agreements in the normal course of business with vendors for preclinical research studies and other services and products for operating purposes.

Under the Invention Management Agreement ("IMA") signed on December 15, 2016, the Company is obligated to share costs related to patent maintenance, defense and prosecution for the CRISPR/Cas9 gene editing intellectual property with California, Vienna and their licensees including Caribou Biosciences, Inc. and Caribou's licensee Intellia Therapeutics, Inc.

Off-Balance Sheet Arrangements

As of December 31, 2018, we do not have any off-balance sheet arrangements, as defined under applicable SEC rules.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our financial statements, which we have prepared in accordance with U.S. generally accepted accounting principles. We believe that several accounting policies are important to understanding our historical and future performance. We refer to these policies as critical because these specific areas generally require us to make judgments and estimates about matters that are uncertain at the time we make the estimate, and different estimates—which also would have been reasonable—could have been used. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and other market-specific or other relevant assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

Revenue

In May 2014, the Financing Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014-09, Revenue from Contracts with Customers ("ASU 2014-09"), which supersedes existing revenue recognition guidance. The Company adopted ASU 2014-09 and its related amendments (collectively known as "ASC 606") on January 1, 2018 using the modified retrospective method, by recognizing the cumulative effect of initially applying ASC 606 as an adjustment to the opening balance of equity at January 1, 2018. The reported results for 2018 reflect the application of ASC 606 guidance while the reported results for 2017 and prior were prepared under the guidance of Accounting Standards Codification ("ASC") 605, Revenue Recognition ("ASC 605"). The Company has elected a practical expedient and applied ASC 606 only to contracts that are not completed at the date of initial application.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. The Company's revenue is from collaboration agreements. Within collaboration agreements, a counterparty may be a collaborator or partner that shares in the risks and benefits of developing a product to be marketed. These arrangements generally are in the scope of ASC 808, Collaborative Arrangements ("ASC 808") yet may also contain vendor-customer aspects. Therefore, the Company considers all of the facts and circumstances to determine which transactions have a vendor-customer relationship that is subject to ASC 606. At the inception of each agreement the Company must determine which promised goods and services are under the scope of ASC 606 versus ASC 808 (discussed in the Collaborative Arrangements note below).

In accordance with 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:

1) Identify the contract with the customer

A contract with a customer exists when (i) the Company enters into an enforceable contract with a customer that defines each party's rights regarding the goods or services to be transferred and identifies the related payment terms, (ii) the contract has commercial substance, and (iii) 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.

2) Identify the performance obligations in the contract

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, whereby the customer can benefit from the good or service either on its own or together with other available resources, and are distinct in the context of the contract, whereby the transfer of the good or service is separately identifiable from other promises in the contract. To the extent a contract includes multiple promised goods and services, the Company must apply judgment to determine whether promised goods and services are 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.

3) Determine the transaction price

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 contracts with customers in Note 9.

4) Allocate the transaction price to performance obligations in the contract

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.

5) Recognize revenue when or as the Company satisfies a performance obligation

The Company satisfies performance obligations either over time or at a point in time. Revenue is recognized over time if either 1) the customer simultaneously receives and consumes the benefits provided by the entity's performance, 2) the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or 3) 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. Examples of control are using the asset to produce goods or services, enhance the value of other assets, settle liabilities, and holding or selling the asset. ASC 606 requires the Company to select a single revenue recognition method for the performance obligation that faithfully depicts the Company's performance in transferring control of the goods and services. The guidance allows entities to choose between two methods to measure progress toward complete satisfaction of a performance obligation:

1. Output methods - recognize revenue on the basis of direct measurements of the value to the customer of the goods or services transferred to date relative to the remaining goods or services promised under the contract (e.g. surveys of performance completed to date, appraisals of results achieved, milestones reached, time elapsed, and units of produced or units delivered); and
2. Input methods - recognize revenue on the basis of the entity's efforts or inputs to the satisfaction of a performance obligation (e.g., resources consumed, labor hours expended, costs incurred, or time elapsed) relative to the total expected inputs to the satisfaction of that performance obligation.

The Company has the right to consideration from a customer in an amount that corresponds directly with the value to the customer of the entity's performance completed to date (i.e. R&D services), as such the Company has elected a practical expedient to recognize revenue in the amount to which the entity has a right to invoice for such services.

The terms of the Company's collaboration and license agreements contain multiple promised goods and services, which include options to license CRISPR/Cas9-based therapeutic products directed to specific targets, referred to as co-exclusive or exclusive licenses, joint steering committee participation, as well as research and development activities to be performed by the Company on behalf of the collaboration partner related to the licensed targets. Payments that the Company may receive under these agreements include nonrefundable upfront fees, payments for research activities, payments based upon the achievement of specified milestones and royalties on any resulting net product sales.

To date, the Company's only source of revenue has been the collaboration and license and joint development and commercialization agreement with Vertex Pharmaceuticals, Incorporated ("Vertex") as well as research and development services provided to Casebia Therapeutics LLP ("Casebia") under the joint venture with Bayer HealthCare LLC ("Bayer"). Please refer to Note 9 for the specific accounting treatment and revenue recognized during the period for each of these arrangements.

Licenses of intellectual property: If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company must consider the nature of the intellectual property to which the customer will have rights (i.e. access at a point in time or benefit of intellectual property enhancements over time). The Company recognizes revenue from non-refundable, up-front fees allocated to the license at a point in time/over the period the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are bundled 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 from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement that includes development, regulatory or commercial milestone payments for promised goods and services, the Company evaluates the circumstances of whether the milestones will be reached and estimates the amount to be included in the transaction price that will not cause a significant revenue reversal. The Company will evaluate these types of payments for customer options once those options have been exercised. ASC 606 suggests two alternatives to use when estimating the amount of variable consideration: the expected value method and the most likely amount method. Under the expected value method, an entity considers the sum of probability-weighted amounts in a range of possible consideration amounts. Under the most likely amount method, an entity considers the single most likely amount in a range of possible consideration amounts. The Company will use the most likely amount method for development and regulatory milestone payments. Management believes the most likely amount method is the better predictor as the Company expects to be entitled to only one of two possible amounts. Additionally, management believes that the most likely amount of milestone consideration is its stated amount. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. The transaction price is then allocated to performance obligations on a specific basis or on a relative stand-alone selling price basis. 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 whether it is probable that a significant revenue reversal will not occur in future periods, and if necessary, adjusts its estimates of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and 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).

Up-front 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 performs its obligations under these arrangements. Amounts payable to the Company are recorded as accounts receivable when the Company's right to consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less.

Contract Balances

The Company recognizes a contract asset when the Company transfers goods or services to a customer before the customer pays consideration or before payment is due, excluding any amounts presented as a receivable (i.e. accounts receivable). A contract asset is an entity's right to consideration in exchange for goods or services that the entity has transferred to a customer. The contract liabilities (i.e. deferred revenue) primarily relate to contracts where we have received payment but we have not yet satisfied the related performance obligations. The advance consideration received from customers for R&D services or licenses bundled with other promises is a contract liability, recorded as deferred revenue, until the underlying performance obligations are transferred to the customer. The change in deferred revenue from December 31, 2017 to December 31, 2018 is primarily related to the transition adjustment upon the adoption of ASC 606.

Income Taxes

The adoption of ASC 606 resulted in a reduction of cumulative revenue as of January 1, 2018, which in turn generated additional deferred tax assets. As the Company fully reserves its net deferred tax assets in the jurisdictions impacted by the adoption of ASC 606, this impact was offset by a corresponding change to the valuation allowance.

Variable Interest Entities

We review each legal entity formed by parties related to the Company to determine whether or not the entity is a Variable Interest Entity ("VIE"), in accordance with the Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 810, Consolidation. If the entity is a VIE, we assess whether or not we are the primary beneficiary of that VIE based on a number of factors, including (i) which party has the power to direct the activities that most significantly affect the VIE's economic performance, (ii) the parties' contractual rights and responsibilities pursuant to any contractual agreements and (iii) which party has the obligation to absorb losses or the right to receive benefits from the VIE. If we determine that we are the primary beneficiary of a VIE, we treat the VIE as a business combination and consolidate the financial statements of the VIE into our consolidated financial statements at the time that determination is made. On a quarterly basis, we evaluate whether it continues to be the primary beneficiary of any consolidated VIEs. If we determine that we are no longer the primary beneficiary of a consolidated VIE, or no longer have a variable interest in the VIE, we deconsolidate the VIE in the period that the determination is made.

If we determine that we are the primary beneficiary of a VIE that meets the definition of a business, we measure the assets, liabilities and non-controlling interests of the newly consolidated entity at fair value in accordance with FASB ASC Topic 805, Business Combinations on the date we become the primary beneficiary.

In February 2016, Casebia Therapeutics LLP, a limited liability partnership, was formed in the United Kingdom. In March 2016 upon consummation of the JV, we and Bayer each received a 50% equity interest in the entity in exchange for our contributions to the entity. We determined that Casebia was considered a VIE and concluded that we are not the primary beneficiary of the VIE. As such, we did not consolidate Casebia's results into the consolidated financial statements. We account for our 50% investment share of Casebia under the equity method of accounting. The formation of Casebia was accounted for at fair value. See Note 9 to the consolidated financial statements for further details relating to the evaluation of Casebia as a VIE as well as our accounting for the formation.

Equity-Based Compensation

We recognize equity-based compensation expense for awards of equity instruments to employees and non-employee directors based on the grant date fair value of those awards in accordance with FASB ASC Topic 718, Stock Compensation ("ASC 718"). ASC 718 requires all equity-based compensation awards to employees and non-employee directors, including grants of restricted shares and stock options, to be recognized as expense in the statements of operations based on their grant date fair values. We estimate the fair value of stock options using the Black-Scholes option pricing model. We use the fair value of our Common Shares to determine the fair value of restricted share awards.

Prior to July 1, 2018, we accounted for stock options issued to non-employees and employees of Casebia under FASB ASC Topic 505-50, Equity Based Payments to Non-Employees ("ASC 505-50") through June 30, 2018. As such, the value of such options were periodically remeasured, and income or expense was recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules was recognized using the straight-line method. As of July 1, 2018, we adopted the FASB issued ASU No. 2018-07, Stock Compensation ("ASU 2018-07") which provides improvements to nonemployee share-based payment accounting. ASU 2018-07 is intended to reduce the cost and complexity and to improve financial reporting for nonemployee share-based payments. The scope of ASC 718, which currently only includes share-based payments to employees was expanded to include share-based payments issued to nonemployees for goods or services. ASC 505-50 was superseded and consequently, the accounting for share-based payments to nonemployees and employees will be substantially aligned. As a result of adopting this standard, the fair value of outstanding nonemployee awards post adoption are no longer remeasured each reporting period and expense related to these awards was recorded based on the fair value measured as of June 30, 2018, the last period prior to the adoption of ASU 2018-07.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected share price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of a public market for the trading of our Common Shares prior to its IPO and a lack of company-specific historical and implied volatility data, we based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies have characteristics similar to us, including stage of product development and focus on the life science industry. We use the simplified method, which is the average of the final vesting tranche date and the contractual term, to calculate the expected term for options granted to employees as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. For options granted to non-employees we utilize the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. We use an assumed dividend yield of zero as we have never paid dividends and has no current plans to pay any dividends on its Common Shares.

We expense the fair value of its equity-based compensation awards granted to employees and non-employees with only service-based vesting on a straight-line basis over the associated service period, which is generally the period in which the related services are received.

We record the expense for equity-based compensation awards subject to performance-based milestone vesting over the remaining service period when management determines that achievement of the milestone is probable. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. We record expense for equity-based compensation awards subject to performance-based vesting conditions using the accelerated attribution method.

The Company uses a Monte Carlo simulation option-pricing model to determine the fair value of market-based awards. The model uses the same input assumptions as the Black-Scholes model, yet, it also incorporates the possibility that the market condition may not be satisfied. Compensation cost related market-based awards are recognized regardless of whether the market condition is satisfied, provided that the requisite service has been provided.

Recent Accounting Pronouncements

Refer to Note 2, "Summary of Significant Accounting Policies," in the accompanying notes to the consolidated financial statements for a discussion of recent accounting pronouncements.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Foreign Exchange Market Risk

As a result of our foreign operations, we face exposure to movements in foreign currency exchange rates, primarily the Swiss Franc and British Pound, against the U.S. dollar. The current exposures arise primarily from cash, accounts payable, and intercompany receivables and payables. Changes in foreign exchange rates affect our consolidated statement of operations and distort comparisons between periods. To date, foreign currency transaction gains and losses have not been material to our financial statements, and we have not engaged in any foreign currency hedging transactions.

Taxation

We are subject to corporate taxation in Switzerland. Under Swiss law, we are entitled to carry forward losses we incur for a period of seven years and we can offset future profits, if any, against such losses. As of December 31, 2017, we reported tax loss carry forwards from inception through 2017 for purposes of Swiss federal direct taxes in the aggregate amount of CHF 103 million. As we moved our legal seat from the Canton of Basel-Stadt to the Canton of Zug mid of 2017, it will be the Canton of Zug, which is in charge for assessing our tax return including our carry forward losses. No ruling regarding taxation as a mixed company has been filed with the Zug tax authorities; however, based on the practice of the Canton of Zug, we can apply for the taxation as mixed company in the tax return as long as the respective law is in force and we fulfill the respective criteria. According to the practice of the Canton of Zug the tax loss carry forwards at cantonal level are the same as at federal level. Therefore, in aggregate as of December 31, 2017 tax loss carry forwards of CHF 103 million have been reported at cantonal level as well. As per January 1, 2018, for the purposes of our Swiss statutory financial statements, we changed our functional currency from CHF to USD. Because Swiss tax laws align with Swiss statutory financial reporting, this resulted in a remeasurement of our Swiss net operating loss carry forwards as of January 1, 2018. According to statutory Swiss accounting law, the translation has to take place at the closing rate as per December 31, 2017. For this purpose, we applied the spot rate of CHF/USD of 1.02438. Although there is no explicit regulation in the law or guideline published by the tax authorities, as the conversion at the closing rate is in accordance with statutory accounting law, it is also to be considered applicable for corporate income tax purposes. Therefore, the tax loss carry forwards as per January 1, 2018 amount to USD 106 million and the tax loss carry forwards as per December 31, 2018 amount to USD 270 million (including the loss 2018 of USD 164 million). It is to be noted in this regard that tax losses are only finally assessed by the tax authorities when offset with taxable profit (which will not be the case as long we are loss making). If not used, these tax losses will expire seven years after the year in which they occurred. Due to our limited income, there is a high risk that the tax loss carry forwards will expire partly or entirely. For 2018, the tax return has, in accordance with Swiss tax law, not yet been filed. Therefore, for 2018 the loss carried forward will only be claimed with filing of the tax return for the tax year 2018.

The statutory corporate profit tax rate in the Canton of Zug amounts to 16.98% (federal, cantonal and communal) of the profit after taxes (taxes are deductible). As already mentioned above, no tax ruling was filed with the Zug tax authorities for applying for the taxation as mixed company. However, as long as the respective law is in force and we fulfill the criteria, a respective application for taxation as a mixed company can be made in the annual tax return and will be granted by the Zug tax authorities. The statutory corporate profit tax rate (on the profit after tax) as mixed company in the Canton of Zug ranges between 9.35% and 10.62% on the profit after taxes (taxes are deductible), depending on the number of full time equivalents employed in Switzerland in a given year. The maximum tax rate applies in case we employ more than 30 full time equivalents by the end of a given year. The Canton does from time to time amend the level of taxation levied on corporations and there is no certainty that the tax rate currently in effect will not change in the future.

The privileges for mixed companies are under pressure and new tax legislations abolish mixed companies but at the same time lowering the ordinary tax rate is in preparation (e.g. the Canton of Zug has announced a planned reduction of its effective income tax rate to 12-12.5% (federal and cantonal)). In May 2019 a public vote on the new tax legislations takes place at Federal level. If accepted, the new legislation may potentially come into force in 2020, whereby changes in the cantonal law may be subject to confirmation by a public vote as well. This cantonal vote may cause a delay on the implementation of lower tax rates at cantonal level.

Item 8. Financial Statements and Supplementary Data.

The consolidated financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15.

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's chief executive officer and chief financial officer, after evaluating the effectiveness of the Company's disclosure controls and procedures (as defined in Rule 13a-15(e) and Rule 15d-15(e) promulgated under the Securities Exchange Act of 1934, as amended) as of the end of the period covered by this Annual Report on Form 10-K, have concluded that, based on such evaluation, the Company's disclosure controls and procedures were effective. In designing and evaluating the disclosure controls and procedures, the Company's management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and the Company's management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control Over Financial Reporting

The management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and Rule 15d-15(f) promulgated under the Securities Exchange Act of 1934, as amended, 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. The Company's internal control over financial reporting 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. 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.

The Company's management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2018. In making this assessment, it used the criteria set forth in the Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework)(COSO). Based on its assessment, the Company's management has concluded that, as of December 31, 2018, the Company's internal control over financial reporting is effective based on those criteria.

The Company's independent registered public accounting firm, Ernst & Young LLP, issued an attestation report on the Company's internal control over financial reporting. See below.

Changes in Internal Control Over Financial Reporting

We use a third party cloud-based software service provider in connection with certain aspects of our financial reporting. In the fourth quarter of 2018, this service provider made changes to its internal controls to address deficiencies in its own information technology change management controls relating to its cloud-based software services.

Other than these third party changes, no change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and the Board of Directors of CRISPR Therapeutics AG

Opinion on Internal Control over Financial Reporting

We have audited CRISPR Therapeutics AG's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, CRISPR Therapeutics AG (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, based on the COSO criteria.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred shares and shareholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2018 and the related notes and our report dated February 25, 2019 expressed an unqualified opinion thereon.

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 Limitation 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 disposition 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 condition, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 25, 2019

Item 9B. Other Information.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item is incorporated by reference to our Proxy Statement for our 2019 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

Item 11. Executive Compensation.

The information required by this item is incorporated by reference to our Proxy Statement for our 2019 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

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

The information required by this item is incorporated by reference to our Proxy Statement for our 2019 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

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

The information required by this item is incorporated by reference to our Proxy Statement for our 2019 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

Item 14. Principal Accounting Fees and Services.

The information required by this item is incorporated by reference to our Proxy Statement for our 2019 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2018.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a)(1) Financial Statements.

See the "Index to Consolidated Financial Statements" on page F-1 below for the list of financial statements filed as part of this report.

(a)(2) Financial Statement Schedules.

I. Financial Statements of Casebia Therapeutics LLP (financial statements required by Regulation S-X).

Schedules other than that listed above have been omitted because of the absence of conditions under which they are required or because the required information is included in the financial statements or the notes thereto.

(a)(3) Exhibits.

The exhibits listed in the Exhibit Index below are filed or incorporated by reference as part of this Annual Report on Form 10-K.

Exhibit Index

Exhibit Number	Description
3.1	Amendment and Restated Articles of Association of CRISPR Therapeutics AG, dated May 30, 2018 (incorporated herein by reference to Exhibit 3.1 to the Company's Quarterly Report on Form 10-Q filed on November 7, 2018).
4.1	Subscription Agreement, dated December 19, 2015, by and between CRISPR Therapeutics AG and Bayer Global Investments B.V. (incorporated herein by reference to Exhibit 4.1 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.1†	Joint Venture Agreement, dated December 19, 2015, between CRISPR Therapeutics AG and Bayer HealthCare LLC (incorporated herein by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.2†	IP Contribution Agreement, dated March 16, 2016, by and between CRISPR Therapeutics AG, Bayer HealthCare LLC and Casebia Therapeutics LLP (incorporated herein by reference to Exhibit 10.2 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.3†	Option Agreement, dated March 16, 2016, by and between CRISPR Therapeutics AG, Bayer HealthCare LLC and Casebia Therapeutics LLP (incorporated herein by reference to Exhibit 10.3 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.4†	Strategic Collaboration, Option and License Agreement, dated October 26, 2015, by and among CRISPR Therapeutics AG, CRISPR Therapeutics Limited, CRISPR Therapeutics, Inc., TRACR Hematology Limited, Vertex Pharmaceuticals, Incorporated and Vertex Pharmaceuticals (Europe) Limited (incorporated herein by reference to Exhibit 10.4 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.5†	License Agreement, dated April 15, 2014, by and between CRISPR Therapeutics AG and Emmanuelle Marie Charpentier (incorporated herein by reference to Exhibit 10.5 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.6†	License Agreement, dated April 15, 2014, by and between TRACR Hematology Limited and Emmanuelle Marie Charpentier (incorporated herein by reference to Exhibit 10.6 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.7†	Patent Assignment Agreement, dated November 7, 2014, by and between CRISPR Therapeutics AG, Emmanuelle Marie Charpentier, the University of Vienna and Ines Fonfara (incorporated herein by reference to Exhibit 10.7 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).

Exhibit Number	Description
10.8	Form of Indemnification Agreement (incorporated herein by reference to Exhibit 10.8 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.9	Registration Rights Agreement, dated June 10, 2016, by and among CRISPR Therapeutics AG and certain shareholders (incorporated herein by reference to Exhibit 10.9 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.10#	Employment Agreement, dated December 1, 2017, by and between CRISPR Therapeutics AG and Rodger Novak (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on December 21, 2017).
10.11#	Second Amended and Restated Employment Agreement, dated October 2, 2017, by and between CRISPR Therapeutics, Inc. and Samarth Kulkarni (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on October 2, 2017).
10.12#	Employment Agreement, dated November 13, 2017, by and between CRISPR Therapeutics, Inc. and Michael Tomsicek (incorporated herein by reference to Exhibit 10.13 to the Company's Annual Report on Form 10-K filed on March 8, 2018).
10.13#	Advisory Agreement, dated December 20, 2017, by and between CRISPR Therapeutics AG and Dr. Anthony Coles (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 21, 2017).
10.14#	Employment Agreement, dated May 31, 2017, by and between CRISPR Therapeutics, Inc. and James R. Kasinger (incorporated herein by reference to Exhibit 10.16 to the Company's Annual Report on Form 10-K filed on March 8, 2018).
10.15#	Employment Agreement, dated August 1, 2017, by and between CRISPR Therapeutics, Inc. and Tony Ho (incorporated herein by reference to Exhibit 10.17 to the Company's Annual Report on Form 10-K filed on March 8, 2018).
10.16#*	Employment Agreement, dated January 2, 2019, by and between CRISPR Therapeutics, Inc. and Lawrence Klein.
10.17#	CRISPR Therapeutics AG 2015 Stock Option and Grant Plan (incorporated herein by reference to Exhibit 10.14 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.18#	CRISPR Therapeutics AG Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on June 2, 2017).
10.18.1#	Form of Incentive Stock Option Agreement under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.18.2#	Form of Non-Qualified Stock Option Agreement for Company Employees under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.3 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.18.3#	Form of Non-Qualified Stock Option Agreement for Non-Employee Directors under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.4 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.18.4#	Form of Restricted Stock Award Agreement under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.5 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.18.5#	Form of Restricted Stock Award Agreement for Company Employees under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.6 to the Company's Current Report on Form 10-Q filed on November 8, 2017).

Exhibit Number	Description
10.18.6#	Form of Restricted Stock Award Agreement for Non-Employee Directors under CRISPR Therapeutics AG's Amended and Restated 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.7 to the Company's Current Report on Form 10-Q filed on November 8, 2017).
10.19#	CRISPR Therapeutics AG 2018 Stock Option and Incentive Plan and forms of agreements thereunder (incorporated herein by reference to Exhibit 99.1 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.19.1#	Form of Incentive Stock Option Agreement under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.2 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.19.2#	Form of Non-Qualified Stock Option Agreement for Company Employees under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.3 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.19.3#	Form of Non-Qualified Stock Option Agreement for Non-Employee Directors under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.4 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.19.4#	Form of Restricted Stock Award under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.5 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.19.5#	Form of Restricted Stock Award Agreement for Company Employees under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.6 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.19.6#	Form of Restricted Stock Award for Non-Employee Directors under CRISPR Therapeutics AG's 2018 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 99.7 to the Company's Registration Statement on Form S-8 filed on June 1, 2018).
10.20#	CRISPR Therapeutics AG 2016 Employee Stock Purchase Plan (incorporated herein by reference to Exhibit 10.16 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.21	Consent to Sublease, dated May 16, 2016, by and between CRISPR Therapeutics, Inc. and Pfizer Inc. (incorporated herein by reference to Exhibit 10.17 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.22†	Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement for a Programmable DNA Restriction Enzyme for Genome Editing, dated December 15, 2016, by and among CRISPR Therapeutics AG, The Regents of the University of California, University of Vienna, Dr. Emmanuelle Charpentier, Intellia Therapeutics, Inc., Caribou Biosciences, Inc., ERS Genomics Ltd., and TRACR Hematology Ltd. (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 16, 2016).
10.23†	Joint Development and Commercialization Agreement by and between, on the one hand, Vertex Pharmaceuticals Incorporated and Vertex Pharmaceuticals (Europe) Limited, and on the other hand, CRISPR Therapeutics AG, CRISPR Therapeutics, Inc., CRISPR Therapeutics Limited and TRACR Hematology Ltd., dated as of December 12, 2017 (incorporated by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 18, 2017).
10.24†	Amendment No. 1 to the Strategic Collaboration, Option and License Agreement by and between, on the one hand, Vertex Pharmaceuticals Incorporated and Vertex Pharmaceuticals (Europe) Limited, and on the other hand, CRISPR Therapeutics AG, CRISPR Therapeutics, Inc., CRISPR Therapeutics Limited and TRACR Hematology Ltd., dated as of December 12, 2017 (incorporated by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K filed on December 18, 2017).
10.25#	Senior Executive Cash Incentive Bonus Plan (incorporated herein by reference to Exhibit 10.26 to the Company's Annual Report on Form 10-K filed on March 8, 2018).

Exhibit Number	Description
10.26†	Research Collaboration Agreement by and between CRISPR Therapeutics AG and ViaCyte, Inc., dated as of September 17, 2018. (incorporated herein by reference to Exhibit 10.1† to the Company's Quarterly Report on Form 10-Q filed on November 7, 2018).
21.1*	Subsidiaries of the Registrant
23.1*	Consent of Ernst & Young LLP
23.2*	Consent of Ernst & Young LLP – Casebia Therapeutics, LLP
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

* Filed herewith.
\+ Furnished herewith.
† Confidential treatment obtained as to certain portions.
\# A management contract or compensatory plan or arrangement required to be filed as an exhibit pursuant to Item 15(a)(3) of Form 10-K.

Item 16. Form 10-K Summary

None.

SIGNATURES

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

CRISPR Therapeutics AG

Date: February 25, 2019

By: /s/ Samarth Kulkarni
Samarth Kulkarni
Chief Executive Officer

SIGNATURES AND POWER OF ATTORNEY

We, the undersigned directors and officers of CRISPR Therapeutics AG (the "Company"), hereby severally constitute and appoint Rodger Novak, Samarth Kulkarni, Michael Tomsicek and James R. Kasinger, and each of them singly, our true and lawful attorneys, with full power to them, and to each of them singly, to sign for us and in our names in the capacities indicated below, any and all amendments to this Annual Report on Form 10-K, and to file or cause to be filed the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as each of us might or could do in person, and hereby ratifying and confirming all that said attorneys, and each of them, or their substitute or substitutes, shall do or cause to be done by virtue of this Power of Attorney.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Samarth Kulkarni Samarth Kulkarni	Chief Executive Officer (Principal Executive Officer)	February 25, 2019
/s/ Michael Tomsicek Michael Tomsicek	Chief Financial Officer (Principal Financial and Accounting Officer)	February 25, 2019
/s/ Rodger Novak Rodger Novak	President and Director	February 25, 2019
/s/ Kurt Von Emster Kurt Von Emster	Director	February 25, 2019
/s/ Ali Behbahani Ali Behbahani	Director	February 25, 2019
/s/ Bradley Bolzon Bradley Bolzon	Director	February 25, 2019
/s/ Pablo Cagnoni Pablo Cagnoni	Director	February 25, 2019
/s/ Simeon J. George Simeon J. George	Director	February 25, 2019
/s/ Thomas Woiwode Thomas Woiwode	Director	February 25, 2019
/s/ Michael Tomsicek Michael Tomsicek	Authorized Representative in the United States	February 25, 2019

CRISPR Therapeutics AG

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and the Board of Directors of CRISPR Therapeutics AG

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of CRISPR Therapeutics AG (the Company) as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred shares and shareholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2018 and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

We also have 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, 2018, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 25, 2019 expressed an unqualified opinion thereon.

Adoption of ASU No. 2014-09, "Revenue from Contracts with Customers"

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2018 due to the adoption of Accounting Standards Update (ASU) No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), and the related amendments.

Adoption of ASU No. 2016-09, "Statement of Cash Flows"

As discussed in Note 2 to the consolidated financial statements, the Company changed its method for presenting restricted cash in the statement of cash flows as a result of the adoption of the amendment to the FASB Accounting Standards Codification resulting from ASU No. 2016-18, *Statement of Cash flows* (Topic 230): Restricted Cash.

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.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2015.
Boston, Massachusetts
February 25, 2019

CRISPR Therapeutics AG
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash	$ 456,649	$ 239,758
Accounts receivable, including related party amounts of $88 and $821 as of December 31, 2018 and 2017, respectively	88	2,626
Prepaid expenses and other current assets, including related party amounts of $3,417 and $1,871 as of December 31, 2018 and 2017, respectively	9,658	6,001
Total current assets	466,395	248,385
Property and equipment, net	18,500	18,857
Intangible assets, net	289	344
Restricted cash	3,163	3,154
Other non-current assets	669	606
Total assets	$ 489,016	$ 271,346
Liabilities and Shareholders' Equity		
Current liabilities:		
Accounts payable	$ 5,069	$ 1,639
Accrued expenses, including related party amounts of $1,700 and $0 as of December 31, 2018 and 2017, respectively	20,852	11,361
Accrued tax liabilities	402	347
Deferred rent	1,202	1,027
Other current liabilities	221	137
Total current liabilities	27,746	14,511
Deferred revenue, including related party amounts of $57,780 and $91 as of December 31, 2018 and 2017, respectively	57,780	56,928
Deferred rent non-current	11,052	11,761
Other non-current liabilities	243	314
Total liabilities	96,821	83,514
Commitments and contingencies (Note 8)		
Shareholders' equity:		
Common shares, CHF 0.03 par value, 52,183,139 and 41,092,969 shares authorized at December 31, 2018 and 2017, respectively, 52,160,798 and 41,037,121 shares issued at December 31, 2018 and 2017, respectively, 51,852,862, and 40,592,248 shares outstanding at December 31, 2018 and 2017, respectively, 20,498,996 and 17,338,291 shares in conditional capital at December 31, 2018 and 2017, respectively.	1,584	1,240
Treasury shares, at cost, 307,936 shares and 444,873 shares at December 31, 2018 and 2017, respectively	(57)	—
Additional paid-in capital	682,245	312,018
Accumulated deficit	(291,569)	(125,440)
Accumulated other comprehensive (loss) income	(8)	14
Total shareholders' equity	392,195	187,832
Total liabilities and shareholders' equity	$ 489,016	$ 271,346

See accompanying notes to these consolidated financial statements.

CRISPR Therapeutics AG
Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share data)

	Years Ended December 31,		
	2018	2017	2016
Collaboration revenue (1)	$ 3,124	$ 40,997	$ 5,164
Operating expenses:			
Research and development (2)	113,773	69,800	42,238
General and administrative	48,294	35,845	31,056
Total operating expenses	162,067	105,645	73,294
Loss from operations	(158,943)	(64,648)	(68,130)
Other (expense) income:			
Interest expense	—	—	(8,050)
Loss from equity method investment	(4,275)	(1,763)	(36,532)
Gain on extinguishment of convertible loan	—	—	11,482
Other (expense) income, net	(1,210)	(197)	78,512
Total other (expense) income, net	(5,485)	(1,960)	45,412
Net loss before provision for from income taxes	(164,428)	(66,608)	(22,718)
Provision for income taxes	(553)	(1,749)	(484)
Net loss	(164,981)	(68,357)	(23,202)
Foreign currency translation adjustment	(22)	40	(18)
Comprehensive loss	$ (165,003)	$ (68,317)	$ (23,220)
Reconciliation of net loss to net loss attributable to common shareholders:			
Net loss	$ (164,981)	$ (68,357)	$ (23,202)
Loss attributable to noncontrolling interest	—	—	25
Net loss attributable to common shareholders	$ (164,981)	$ (68,357)	$ (23,177)
Net loss per share attributable to common shareholders—basic and diluted	$ (3.44)	$ (1.71)	$ (1.89)
Weighted-average common shares outstanding used in net loss per share attributable to common shareholders—basic and diluted	47,964,368	40,057,365	12,257,483
(1) Including the following amounts of revenue from a related party, see Note 15:	$ 3,124	$ 4,760	$ 1,190
(2) Including the following amounts of research and development from a related party, see Note 15:	$ 23,982	$ 4,523	$ 1,755

See accompanying notes to these consolidated financial statements.

CRISPR Therapeutics AG
Consolidated Statements of Redeemable Convertible Preferred Shares and Shareholders' (Deficit) Equity
(In thousands, except share and per share data)

	Series A-1 Redeemable Convertible Preferred Shares		Series A-2 Redeemable Convertible Preferred Shares		Series A-3 Redeemable Convertible Preferred Shares		Series B Redeemable Convertible Preferred Shares		Common Shares		Treasury Shares					Total CRISPR Therapeutics AG Shareholders' (Deficit) Equity		Total Shareholders' (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	CHF 0.03 Par Value	Shares	Amount, at cost	Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)		Noncontrolling Interest	
Balance at December 31, 2015	440,001	$ 1,169	3,120,001	$ 10,394	10,758,006	$ 22,518	4,519,016	$ 30,440	5,528,079	$ 181	—	—	$ 4,636	$ (33,906)	$ (8)	$ (29,097)	$ (27)	$ (29,124)
Conversion of Convertible Loans	—	—	—	—	—	—	5,464,608	61,929	—	—	—	—	—	—	—	—	—	—
Receipt of Series A-3 Subscription Receivable	—	—	—	—	—	22,850	—	—	—	—	—	—	—	—	—	—	—	—
Issuance of Series B Preferred Shares, net of issuance costs of $1.8 million	—	—	—	—	—	—	2,834,252	36,265	—	—	—	—	—	—	—	—	—	—
Conversion of redeemable convertible preferred shares into common share	(440,001)	(1,169)	(3,120,001)	(10,394)	(10,758,006)	(45,368)	(12,817,876)	(128,634)	27,135,884	823			184,742			185,565		185,565
Adjustment to Noncontrolling interest upon share exchange for TRACR	—	—	—	—	—	—	—	—	328,017	10			(62)			(52)	52	—
Issuance of common stock, net of issuance costs of $8.3 million	—	—	—	—	—	—	—	—	7,100,000	213			88,451			88,664		88,664
Repurchase of treasury shares	—	—	—	—	—	—	—	—	(444,873)	(13)	444,873	—	13	—	—	—	—	—
Vesting of restricted shares									53,427	1			81			82		82
Exercise of vested options	—	—	—	—	—	—	—	—	18,900	1	—	—	34	—	—	35	—	35
Stock- based compensation expense	—	—	—	—	—	—	—	—	—	—	—	—	10,844	—	—	10,844	—	10,844
Other comprehensive income (loss)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(18)	(18)	—	(18)
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	(23,177)	—	(23,177)	(25)	(23,202)
Balance at December 31, 2016	—	$ —	—	$ —	—	$ —	—	$ —	39,719,434	$ 1,216	444,873	$ —	$ 288,739	$ (57,083)	$ (26)	$ 232,846	$ —	$ 232,846
Vesting of restricted shares							—	—	33,519	1	—	—	58	—	—	59	—	59
Exercise of vested options	—	—	—	—	—	—	—	—	839,295	23	—	—	2,585	—	—	2,608	—	2,608
Stock- based compensation expense	—	—	—	—	—	—	—	—	—	—	—	—	20,636	—	—	20,636	—	20,636
Other comprehensive income (loss)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	40	40	—	40
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	(68,357)	—	(68,357)	—	(68,357)
Balance at December 31, 2017	—	$ —	—	$ —	—	$ —	—	$ —	40,592,248	$ 1,240	444,873	$ —	$ 312,018	$ (125,440)	$ 14	$ 187,832	$ —	$ 187,832
Cumulative effect of ASC 606 adoption									—	—	—	—	—	(1,148)	—	(1,148)		$ (1,148)
Issuance of common stock, net of issuance costs of $23.8 million									9,960,526	311	—	—	306,742	—	—	307,053		$ 307,053
Vesting of restricted shares							—	—	38,761	1	—	—	112	—	—	113	—	113
Exercise of vested options, net of issuance costs of $0.4 million	—	—	—	—	—	—	—	—	946,131	26	(36,253)	—	8,537	—	—	8,563	—	8,563
Repurchase of treasury shares									(64,952)	—	64,952	(57)	—	—	—	(57)		(57)
Issuance of shares to ViaCyte									380,148	6	(165,636)	—	15,576	—	—	15,582		15,582
Stock- based compensation expense	—	—	—	—	—	—	—	—	—	—	—	—	39,260	—	—	39,260	—	39,260
Other comprehensive loss	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(22)	(22)	—	(22)
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	(164,981)	—	(164,981)	—	(164,981)
Balance at December 31, 2018	—	$ —	—	$ —	—	$ —	—	$ —	51,852,862	$ 1,584	307,936	(57)	$ 682,245	$ (291,569)	$ (8)	$ 392,195	$ —	$ 392,195

See accompanying notes to these consolidated financial statements.

CRISPR Therapeutics AG
Consolidated Statements of Cash Flows
(In thousands)

	Years Ended December 31,		
	2018	2017	2016
Operating activities			
Net loss	$ (164,981)	$ (68,357)	$ (23,202)
Reconciliation of net loss to net cash used in operating activities:			
Depreciation and amortization	3,519	3,024	925
Equity-based compensation	34,985	18,873	10,844
Non-cash interest	—	—	8,050
Unrealized foreign currency remeasurement (gain) loss	—	(9)	2
Gain on extinguishment of convertible loan	—	—	(11,482)
Other income - formation of joint venture	—	—	(78,608)
Loss from equity method investment	4,275	1,763	36,380
Non-cash expense related to ViaCyte transaction	15,582	—	—
Other income, non-cash	(169)	—	—
Changes in:			
Accounts receivable	2,538	531	(2,818)
Prepaid expenses and other assets	(3,342)	(4,117)	(1,071)
Accounts payable and accrued expenses	12,110	(831)	3,860
Deferred revenue	(296)	(20,718)	1,917
Deferred rent	(709)	(522)	2,360
Other liabilities, net	249	270	(17)
Net cash used in operating activities	(96,239)	(70,093)	(52,860)
Investing activities			
Purchase of property and equipment	(2,773)	(7,814)	(3,016)
Proceeds from contribution of intellectual property to equity method investee	—	—	35,000
Cash investment in equity method investee	—	—	(100)
Purchase of available for sale debt security	—	(500)	—
Net cash (used in) provided by investing activities	(2,773)	(8,314)	31,884
Financing activities			
Proceeds from issuance of common shares, net of issuance costs	307,053	0	89,061
Proceeds from exercise of options	8,938	2,608	34
Repurchase of common shares	(57)	—	—
Proceeds from issuance of Series A-3 preferred shares	—	—	22,850
Proceeds from issuance of Series B preferred shares	—	—	38,075
Issuance costs for preferred share financings	—	—	(1,810)
Proceeds from issuance of convertible loans	—	—	35,010
Net cash provided by financing activities	315,934	2,608	183,220
Effect of exchange rate changes on cash	(22)	41	(235)
Increase (decrease) in cash and restricted cash	216,900	(75,758)	162,009
Cash, cash equivalents and restricted cash, beginning of period	242,912	318,670	156,661
Cash, cash equivalents and restricted cash, end of period	$ 459,812	$ 242,912	$ 318,670
Supplemental disclosure of non-cash investing and financing activities			
Property and equipment purchases in accounts payable and accrued expenses	$ 334	$ —	$ 7,014
Stock option issuance costs included in accrued expenses	$ 375	$ —	$ —
Costs for proposed supplemental offering in accounts payable and accrued expenses	$ —	$ 290	$ —
Property and equipment related to lease incentives	$ —	$ —	$ 10,785
Conversion of preferred shares to common shares upon IPO	$ —	$ —	$ 185,565
Conversion of Vertex and Bayer convertible loans and accrued interest	$ —	$ —	$ 61,929
Issuance costs for public offering in accounts payable and accrued expenses	$	$	$ 397
Contribution of intellectual property to Casebia	$	$	$ 36,380

See accompanying notes to these consolidated financial statements.

1. Organization and Operations

Nature of business

CRISPR Therapeutics AG ("CRISPR" or the "Company") was formed on October 28, 2013 in Basel, Switzerland. The Company was established to translate CRISPR/Cas9, a genome editing technology, into transformative gene-based medicines for the treatment of serious human diseases. The foundational intellectual property underlying the Company's operations was licensed to the Company and its subsidiaries in April 2014. The Company devotes substantially all of its efforts to product research and development activities, initial market development and raising capital. The Company's principal offices are in Zug, Switzerland and operations are in Cambridge, Massachusetts.

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any drug product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations and ability to transition from pilot-scale manufacturing to large-scale production of products.

The Company had an accumulated deficit of $291.6 million as of December 31, 2018 and has financed its operations to date from proceeds obtained from its IPO, subsequent offerings of its common shares in January 2018 and September 2018, a series of preferred shares and convertible loan issuances, and upfront fees received under its collaboration and joint venture arrangements. The Company will require substantial additional capital to fund its research and development and ongoing operating expenses.

Liquidity

In January 2018, the Company completed an offering of 5,750,000 shares of common shares, which were sold at a price of $22.75 per share. This offering resulted in net proceeds of $122.6 million. In August 2018, the Company entered into an At-The-Market ("ATM") sales agreement with Jefferies LLC ("Jefferies"), under which the Company may offer and sell from time to time common shares having aggregate gross proceeds of up to $125.0 million. The Company has not yet issued or sold any securities under this sales agreement. In September 2018, the Company completed an offering of 4,210,526 common shares, which were sold at a price to the public of $47.50 per share. This offering resulted in net proceeds of $187.6 million. In addition, the issuance proceeds from the January and September offerings were further reduced by $3.1 million of stamp taxes, which were recorded as an offset to additional paid in capital. The Company believes its cash of $456.6 million at December 31, 2018 will be sufficient to fund the Company's current operating plan for at least the next 24 months. Thereafter, the Company will be required to obtain additional funding. There can be no assurances, however, that the current operating plan will be achieved or that additional funding will be available on terms acceptable to the Company, or at all.

2. Summary of Significant Accounting Policies and basis of presentation

Basis of Presentation and Use of Estimates

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of (i) the Company, (ii) its wholly-owned subsidiaries, CRISPR Therapeutics Ltd., CRISPR Therapeutics Inc., CTX Financing GmbH, and TRACR Hematology Ltd., as of December 31, 2018. All intercompany accounts and transactions have been eliminated. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

Investments in partnerships where the Company has significant influence because it has a voting interest of 20% to 50%, are accounted for under the equity method. Results of associated companies are presented on a one-line basis. The Company accounts for its 50% investment share of Casebia Therapeutics LLP ("Casebia") under the equity method of accounting. See Note 9 for further details.

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, equity-based compensation expense, revenue recognition, equity method investments, and reported amounts of expenses during the reported period. Significant estimates in these consolidated financial statements have been made in connection with the calculation of revenues, research and development expenses, valuation of equity

method of investment, equity-based compensation expense, fair value of Common Shares, and the provision for or benefit from income taxes. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Actual results may differ from those estimates or assumptions.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company and the Company's chief operating decision maker, namely, the chief executive officer, view the Company's operations and manage its business in one operating segment, which is the business of discovering, developing and commercializing therapies derived from or incorporating genome-editing technology.

Foreign Currency Translation and Transactions

The Company's reporting currency is the U.S. Dollar. The Company's consolidated entities have the U.S. dollar as their functional currency with the exception of CRISPR Ltd. which has the British Pound Sterling ("GBP") as its functional currency. CRISPR Ltd. has assets and liabilities translated into U.S. dollars at exchange rates in effect at the end of the year. Revenue and expenses are translated using the average exchange rates for the period. Net unrealized gains and losses resulting from foreign currency translation are included in accumulated other comprehensive loss, which is a separate component of shareholders' equity. Net foreign currency exchange transaction gains and losses resulting from the remeasurement of transactions denominated in currencies other than functional currency are included in other (expense) income, net in the consolidated statements of operations and comprehensive loss.

Cash and Cash Equivalents

The Company considers all highly liquid investments with maturities of 90 days or less from the purchase date to be cash equivalents. As of December 31, 2018 and 2017, the Company had $456.6 million and $239.8 million in cash equivalents, respectively. The Company considers all highly liquid investments with original maturities of three months or less at the date of purchase to be cash equivalents.

Restricted Cash

In 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230) Restricted Cash* ("ASU 2016-18"), which requires that a statement of cash flows explain the change during the period in the total of cash, cash equivalents and restricted cash. Therefore, amounts described as restricted cash should be included with cash and cash equivalents when reconciling the beginning of period and end of period amounts shown on the statement of cash flows. The amended guidance became effective January 1, 2018 and is effective on a retrospective basis and as such, prior year balances related to restricted cash have been reclassified. Cash, cash equivalents and restricted cash at the end of each period presented in the Company's consolidated statements of cash flows consisted of the following:

	As of December 31,		
	2018	2017	2016
Cash and cash equivalents	456,649	239,758	315,520
Restricted Cash	3,163	3,154	3,150
Total	$ 459,812	$ 242,912	$ 318,670

Accounts Receivable

Accounts receivable of $0.1 million and $2.6 million at December 31, 2018 and 2017, respectively, consist of receivables from Vertex Pharmaceuticals, Incorporated ("Vertex") and Casebia. These amounts represent the balance due from the respective parties for the portion of our arrangements accounted for under ASC 606, *Revenue from contracts with customers.* Vertex and Casebia are creditworthy entities that maintain an ongoing relationship with the Company, as such the Company did not have an allowance for estimated losses recorded related to these receivables.

Other Receivables

Other receivables of $3.4 million and $1.9 million at December 31, 2018 and 2017, respectively, consists of receivables from Vertex and are included with prepaid and other expense in the consolidated balance sheet. These amounts represent the balance due from the portion of our arrangement accounted for under ASC 808, *Collaborative Arrangements*. Receivables are recorded at invoiced amounts

due under the Vertex collaboration agreement (see Note 9). Vertex is a creditworthy entity that maintain an ongoing relationship with the Company, as such the Company did not have an allowance for estimated losses recorded related to these receivables.

Concentrations of Credit Risk and Off-balance Sheet Risk

Financial instruments that potentially subject the Company to concentrations of credit risk are primarily cash. The Company's cash is held in accounts with financial institutions that management believes are creditworthy. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has no financial instruments with off-balance sheet risk of loss.

Fair Value of Financial Instruments

The Company's financial instruments consist of accounts payable, accrued expenses and other non-current liabilities. The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. FASB ASC Topic 820, *Fair Value Measurement and Disclosures* ("ASC 820"), established a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available. Observable inputs are inputs that market participants would use in pricing the financial instrument based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the financial instrument and are developed based on the best information available in the circumstances.

The accounting standard describes a fair value hierarchy based on three levels of inputs, of which the first two are considered observable and the last unobservable, that may be used to measure fair value, which are the following:

Level 1 — Quoted prices in active markets that are accessible at the market date for identical unrestricted assets or liabilities.

Level 2 — Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs for which all significant inputs are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

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.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amount of accounts receivable, other receivables, accounts payable, and accrued expenses as reported on the consolidated balance sheets as of December 31, 2018 and 2017, approximate fair value, due to the short-term duration of these instruments.

The fair value of the Company's equity method investment in Casebia was determined using level 3 inputs (See Note 9).

Property and Equipment

Property and equipment is stated at cost, less accumulated depreciation. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon disposal, the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss is included in the results of operations. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets, which are as follows:

Asset	Estimated useful life
Computer equipment	3 years
Furniture, fixtures, and other	5 years
Laboratory equipment	5 years
Leasehold improvements	Shorter of useful life or remaining lease term

Impairment of Long-lived Assets

The Company evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparing the book value of the assets to the

expected future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value. The Company has not recognized any impairment losses in the years ended December 31, 2018, 2017, and 2016.

Revenue Recognition

In May 2014, the FASB issued ASU No. 2014-09, Revenue from Contracts with Customers ("ASU 2014-09"), which supersedes existing revenue recognition guidance. The Company adopted ASU 2014-09 and its related amendments (collectively known as "ASC 606") on January 1, 2018 using the modified retrospective method, by recognizing the cumulative effect of initially applying ASC 606 as an adjustment to the opening balance of equity at January 1, 2018. The reported results for 2018 reflect the application of ASC 606 guidance while the reported results for 2017 and prior were prepared under the guidance of ASC 605, Revenue Recognition ("ASC 605"). The Company has elected a practical expedient and applied ASC 606 only to contracts that are not completed at the date of initial application.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments. The Company's revenue is from collaboration agreements. Within collaboration agreements, a counterparty may be a collaborator or partner that shares in the risks and benefits of developing a product to be marketed. These arrangements generally are in the scope of ASC 808, Collaborative Arrangements ("ASC 808") yet may also contain vendor-customer aspects. Therefore, the Company considers all of the facts and circumstances to determine which transactions have a vendor-customer relationship that is subject to ASC 606. At the inception of each agreement the Company must determine which promised goods and services are under the scope of ASC 606 versus ASC 808 (discussed in the Collaborative Arrangements note below).

In accordance with 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:

1) Identify the contract with the customer

A contract with a customer exists when (i) the Company enters into an enforceable contract with a customer that defines each party's rights regarding the goods or services to be transferred and identifies the related payment terms, (ii) the contract has commercial substance, and (iii) 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.

2) Identify the performance obligations in the contract

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, whereby the customer can benefit from the good or service either on its own or together with other available resources, and are distinct in the context of the contract, whereby the transfer of the good or service is separately identifiable from other promises in the contract. To the extent a contract includes multiple promised goods and services, the Company must apply judgment to determine whether promised goods and services are 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.

3) Determine the transaction price

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 contracts with customers in Note 9.

4) Allocate the transaction price to performance obligations in the contract

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.

5) Recognize revenue when or as the Company satisfies a performance obligation

The Company satisfies performance obligations either over time or at a point in time. Revenue is recognized over time if either 1) the customer simultaneously receives and consumes the benefits provided by the entity's performance, 2) the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or 3) 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. Examples of control are using the asset to produce goods or services, enhance the value of other assets, settle liabilities, and holding or selling the asset. ASC 606 requires the Company to select a single revenue recognition method for the performance obligation that faithfully depicts the Company's performance in transferring control of the goods and services. The guidance allows entities to choose between two methods to measure progress toward complete satisfaction of a performance obligation:

1. Output methods - recognize revenue on the basis of direct measurements of the value to the customer of the goods or services transferred to date relative to the remaining goods or services promised under the contract (e.g. surveys of performance completed to date, appraisals of results achieved, milestones reached, time elapsed, and units of produced or units delivered); and
2. Input methods - recognize revenue on the basis of the entity's efforts or inputs to the satisfaction of a performance obligation (e.g., resources consumed, labor hours expended, costs incurred, or time elapsed) relative to the total expected inputs to the satisfaction of that performance obligation.

The Company has the right to consideration from a customer in an amount that corresponds directly with the value to the customer of the entity's performance completed to date (i.e. R&D services), as such the Company has elected a practical expedient to recognize revenue in the amount to which the entity has a right to invoice for such services.

The terms of the Company's collaboration and license agreements contain multiple promised goods and services, which include options to license CRISPR/Cas9-based therapeutic products directed to specific targets, referred to as co-exclusive or exclusive licenses, joint steering committee participation, as well as research and development activities to be performed by the Company on behalf of the collaboration partner related to the licensed targets. Payments that the Company may receive under these agreements include nonrefundable upfront fees, payments for research activities, payments based upon the achievement of specified milestones and royalties on any resulting net product sales.

To date, the Company's only source of revenue has been the collaboration and license and joint development and commercialization agreement with Vertex as well as research and development services provided to Casebia under the joint venture with Bayer HealthCare LLC ("Bayer"). Please refer to Note 9 for the specific accounting treatment and revenue recognized during the period for each of these arrangements.

Licenses of intellectual property: If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company must consider the nature of the intellectual property to which the customer will have rights (i.e. access at a point in time or benefit of intellectual property enhancements over time). The Company recognizes revenue from non-refundable, up-front fees allocated to the license at a point in time/over the period the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are bundled 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 from non-refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement that includes development, regulatory or commercial milestone payments for promised goods and services, the Company evaluates the circumstances of whether the milestones will be reached and estimates the amount to be included in the transaction price that will not cause a significant revenue reversal. The Company will evaluate these types of payments for customer options once those options have been exercised. ASC 606 suggests two alternatives to use when estimating the amount of variable consideration: the expected value method and the most likely amount method. Under the expected value method, an entity considers the sum of probability-weighted amounts in a range of possible consideration amounts. Under the most likely amount method, an entity considers the single most likely amount in a range of possible consideration amounts. The Company will use the most likely amount method for development and regulatory milestone payments. Management believes the most likely amount method is the better predictor as the Company expects to be entitled to only one of two possible amounts. Additionally, management believes that the most likely amount of milestone consideration is its stated amount. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. The transaction price is then allocated to performance obligations on a specific basis or on a relative stand-alone selling price basis. 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 whether it is probable that a significant revenue reversal will not occur in future periods, and if necessary, adjusts its estimates of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and 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).

Up-front 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 performs its obligations under these arrangements. Amounts payable to the Company are recorded as accounts receivable when the Company's right to consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less.

Contract Balances

The Company recognizes a contract asset when the Company transfers goods or services to a customer before the customer pays consideration or before payment is due, excluding any amounts presented as a receivable (i.e. accounts receivable). A contract asset is an entity's right to consideration in exchange for goods or services that the entity has transferred to a customer. The contract liabilities (i.e. deferred revenue) primarily relate to contracts where we have received payment but we have not yet satisfied the related performance obligations. The advance consideration received from customers for R&D services or licenses bundled with other promises is a contract liability, recorded as deferred revenue, until the underlying performance obligations are transferred to the customer. The change in deferred revenue from December 31, 2017 to December 31, 2018 is primarily related to the transition adjustment upon the adoption of ASC 606.

Income Taxes

The adoption of ASC 606 resulted in a reduction of cumulative revenue as of January 1, 2018, which in turn generated additional deferred tax assets. As the Company fully reserves its net deferred tax assets in the jurisdictions impacted by the adoption of ASC 606, this impact was offset by a corresponding change to the valuation allowance.

Impact of Adopting ASC 606 on the Financial Statements

The Company adopted ASC 606 using the modified retrospective method. The cumulative effect of applying the new guidance to all contracts with customers that were not completed as of January 1, 2018 was recorded as an adjustment to accumulated deficit as of the adoption date. The Company elected to apply a practical expedient to reflect the aggregate effect of all modifications that occur before the beginning of the earliest period presented when identifying the satisfied and unsatisfied performance obligations, determining the transaction price, and allocating the transaction price to the satisfied and unsatisfied performance obligations. As a result of applying the modified retrospective method to adopt the new revenue guidance, the following adjustments were made to the consolidated balance sheet as of January 1, 2018:

	As Reported December 31, 2017	ASC 606 Adjustment	Adjusted January 1, 2018
Consolidated Balance Sheet Data (in thousands):			
Other current liabilities	$ 137	$ 102	$ 239
Total current liabilities	$ 14,511	$ 102	$ 14,613
Deferred revenue	$ 56,928	$ 1,046	$ 57,974
Total liabilities	$ 83,514	$ 1,148	$ 84,662
Accumulated deficit	$ (125,440)	$ (1,148)	$ (126,588)
Total shareholders' equity	$ 187,832	$ (1,148)	$ 186,684
Total liabilities and shareholders' equity	$ 271,346	$ —	$ 271,346

Impact of New Revenue Guidance on Financial Statement Line Items

The following table compares the reported condensed consolidated balance sheet, statement of operations and cash flows, as of and for the year ended December 31, 2018, to the pro-forma amounts had the previous guidance been in effect:

	As of December 31, 2018			
	As Reported Under ASC 606	Adjustments	Notes	Adjusted Balance Under ASC 605
Consolidated Balance Sheet Data (in thousands):				
Other current liabilities	$ 221	$ (102)	(5)	$ 119
Total current liabilities	$ 27,746	$ (102)	(5)	$ 27,644
Deferred revenue	$ 57,780	$ (750)	(1)(2)(3)(5)	$ 57,030
Total liabilities	$ 96,821	$ (852)	(1)(2)(3)(5)	$ 95,969
Accumulated deficit	$ (291,569)	$ 852	(1)(2)(3)	$ (290,717)
Total shareholders' equity	$ 392,195	$ 852	(1)(2)(3)	$ 393,047
Total liabilities and shareholders' equity	$ 489,016	$ —	(1)(2)(3)	$ 489,016

	Year Ended December 31, 2018			
Consolidated Statement of Operations Data (in thousands):	As Reported Under ASC 606	Adjustments	Notes	Adjusted Balance Under ASC 605
Collaboration revenue	$ 3,124	$ (296)	(2)(3)	$ 2,828
Loss from operations	$ (158,943)	$ (296)	(2)(3)	$ (159,239)
Net loss before income taxes	$ (164,428)	$ (296)	(2)(3)	$ (164,724)
Net loss	$ (164,981)	$ (296)	(2)(3)	$ (165,277)
Comprehensive loss	$ (165,003)	$ (296)	(2)(3)	$ (165,299)
Consolidated Statement of Cash Flows (in thousands):				
Operating activities:				
Net loss	$ (164,981)	$ (296)	(2)(3)	$ (165,277)
Reconciliation of net loss to net cash and restricted cash used in operating activities:				
Changes in:				
Deferred revenue	$ (296)	$ 398	(1)(2)(3)(4)(5)	$ 102
Other liabilities, net	$ 249	$ (102)	(1)(2)(3)(4)(5)	$ 147
Net cash and restricted cash (used in) operating activities	$ (96,239)	$ —		$ (96,239)
Increase (decrease) in cash and restricted cash	$ 216,900	$ —		$ 216,900
Cash and restricted cash, end of period	$ 459,812	$ —		$ 459,812

(1) Adjustment of $1,148 to reverse the ASC 606 transition adjustment from accumulated deficit and deferred revenue.
(2) Adjustment of $194 for the year ended December 31, 2018, related to R&D services that would be deferred under ASC 605 versus recognized as invoiced under ASC 606.
(3) Adjustment of $102 for the year ended December 31, 2018, related to non-exclusive research license revenue that would be recognized upon option exercise under ASC 605 versus recognized overtime under ASC 606.
(4) Adjustment to reverse the ASC 606 transition adjustment to accumulated deficit and deferred revenue netted to zero as the transaction did not impact cash.
(5) Adjustment to reclassify $102 from deferred revenue to other current liabilities (current deferred revenue) related to the change in revenue allocated to the non-exclusive research license recognized upon option exercise under ASC 605 versus ratably over time under ASC 606.

Collaboration Arrangements

The Company records the elements of its collaboration agreements that represent joint operating activities in accordance with ASC 808. Accordingly, the elements of the collaboration agreements that represent activities in which both parties are active participants and to which both parties are exposed to the significant risks and rewards that are dependent on the commercial success of

the activities, are recorded as collaborative arrangements. The Company considers the guidance in ASC 606 in determining the appropriate treatment for the transactions between the Company and its collaborative partner and the transactions between the Company and third parties. Generally, the classification of transactions under the collaborative arrangements is determined based on the nature and contractual terms of the arrangement along with the nature of the operations of the participants.

The Company evaluates the proper presentation of the commercial activities and the profit and loss sharing associated with the collaboration agreements. ASC 808 states that when payments between parties in a collaborative arrangement are not within the scope of other authoritative accounting literature, the income statement classification should be based on the nature of the arrangement, the nature of its business operations and the contractual terms of the arrangement. To the extent that these payments are not within the scope of other authoritative accounting literature, the income statement classification for the payments shall be based on an analogy to authoritative accounting literature or if there is no appropriate analogy, a reasonable, rational, and consistently applied accounting policy election.

Research and Development Expenses

Research and development costs, which include employee compensation costs, facilities, lab supplies and materials, overhead, preclinical development, and other related costs, are charged to expense as incurred. Research and development costs also include the costs the Company incurs in its performance of services or provision of materials in connection with the funded research undertaken as a part of the Company's collaborative agreement with Vertex and Casebia. See Note 9 for further details.

Operating Leases

The Company leases office and laboratory facilities under a non-cancelable operating lease agreements. The lease agreements contain free or escalating rent payment provisions. The Company recognizes rent expense under such leases on a straight-line basis over the term of the lease with the difference between the expense and the payments recorded as deferred rent on the consolidated balance sheets. Lease renewal periods are considered on a lease-by-lease basis in determining the lease term. Funding of leasehold improvements by the Company's landlord are accounted for as a tenant improvement allowance and are amortized as a reduction of rent expense over the term of the lease. Leasehold improvements are amortized straight-line over the shorter of the useful life or the remaining lease term.

Equity Based Compensation Expense

The Company recognizes equity-based compensation expense for awards of equity instruments to employees and non-employee directors based on the grant date fair value of those awards in accordance with FASB ASC Topic 718, Stock Compensation ("ASC 718"). ASC 718 requires all equity-based compensation awards to employees and non-employee directors, including grants of restricted shares and stock options, to be recognized as expense in the statements of operations based on their grant date fair values. The Company estimates the fair value of stock options using the Black-Scholes option pricing model. The Company uses the fair value of our Common Shares to determine the fair value of restricted share awards.

Prior to July 1, 2018, the Company accounted for stock options issued to non-employees and employees of Casebia under FASB ASC Topic 505-50, Equity Based Payments to Non-Employees ("ASC 505-50") through June 30, 2018. As such, the value of such options were periodically remeasured, and income or expense was recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules was recognized using the straight-line method. As of July 1, 2018, the Company adopted the FASB ASU No. 2018-07, Stock Compensation ("ASU 2018-07") which provides improvements to nonemployee share-based payment accounting. ASU 2018-07 is intended to reduce the cost and complexity and to improve financial reporting for nonemployee share-based payments. The scope of ASC 718, which currently only includes share-based payments to employees was expanded to include share-based payments issued to nonemployees for goods or services. ASC 505-50, was superseded and consequently, the accounting for share-based payments to nonemployees and employees will be substantially aligned. As a result of adopting this standard, the fair value of outstanding nonemployee awards post adoption are no longer remeasured each reporting period and expense related to these awards was recorded based on the fair value measured as of June 30, 2018, the last period prior to the adoption of ASU 2018-07.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected share price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of a public market for the trading of the Company's Common Shares prior to its IPO and a lack of company-specific historical and implied volatility data, the Company based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies have characteristics similar to the Company, including stage of product development and focus on the life science industry. The Company uses the simplified method, which is the average of the

final vesting tranche date and the contractual term, to calculate the expected term for options granted to employees as the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. For options granted to non-employees the Company utilizes the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The Company assumed a dividend yield of zero as we have never paid dividends and has no current plans to pay any dividends on its Common Shares.

The Company expenses the fair value of its equity-based compensation awards granted to employees and non-employees with only service-based vesting on a straight-line basis over the associated service period, which is generally the period in which the related services are received.

The Company records the expense for equity-based compensation awards subject to performance-based milestone vesting over the remaining service period when management determines that achievement of the milestone is probable. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. The Company records expense for equity-based compensation awards subject to performance-based vesting conditions using the accelerated attribution method.

The Company uses a Monte Carlo simulation option-pricing model to determine the fair value of market-based awards. The model uses the same input assumptions as the Black-Scholes model, yet, it also incorporates the possibility that the market condition may not be satisfied. Compensation cost related market-based awards are recognized regardless of whether the market condition is satisfied, provided that the requisite service has been provided.

Patent Costs

Costs to secure and prosecute patent application and other legal costs related to the protection of the Company's intellectual property are expensed as incurred and are classified as general and administrative expenses in the Company's consolidated statements of operations.

Income Taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and tax reporting basis of assets and liabilities and are measured using enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The Company has evaluated available evidence and concluded that the Company may not realize all the benefit of its deferred tax assets; therefore, a valuation allowance has been established for the amount of the deferred tax assets that the Company does not believe is more likely than not to be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2018 and 2017, the Company does not have any significant uncertain tax positions. The Company's practice is to recognize interest and/or penalties related to income tax matters in income tax expense. See Note 14 for further details.

Comprehensive Loss

Comprehensive loss consists of net income or loss and changes in equity during the period from transactions and other events and circumstances generated from non-owner sources. The Company's net loss equals comprehensive loss, net of any changes in the foreign currency translation adjustment, for all periods presented. In addition, comprehensive loss attributable to the noncontrolling interest equals net loss for all periods presented.

Variable Interest Entities

The Company reviews each legal entity formed by parties related to the Company to determine whether or not the Company has a variable interest in the entity and whether or not the entity would meet the definition of a VIE in accordance with FASB ASC Topic 810, *Consolidation* ("ASC 810"). If the entity is a VIE, the Company assesses whether or not the Company is the primary beneficiary of that VIE based on a number of factors, including (i) which party has the power to direct the activities that most significantly affect the VIE's economic performance, (ii) the parties' contractual rights and responsibilities pursuant to any contractual agreements and

(iii) which party has the obligation to absorb losses or the right to receive benefits from the VIE. If the Company determines it is the primary beneficiary of a VIE, the Company consolidates the financial statements of the VIE into the Company's consolidated financial statements at the time that determination is made. The Company evaluates whether it continues to be the primary beneficiary of any consolidated VIEs on a quarterly basis. If the Company were to determine that it is no longer the primary beneficiary of a consolidated VIE, or no longer has a variable interest in the VIE, it would deconsolidate the VIE in the period that the determination is made.

If the Company determines it is the primary beneficiary of a VIE that meets the definition of a business, the Company measures the assets, liabilities and noncontrolling interests of the newly consolidated entity at fair value in accordance with FASB ASC Topic 805, *Business Combinations* ("ASC 805") at the date the reporting entity first becomes the primary beneficiary.

In February 2016, Casebia Therapeutics LLP, a limited liability partnership, was formed in the United Kingdom. In March 2016 upon consummation of the JV, Bayer and the Company each received a 50% equity interest in the entity in exchange for their contributions to the entity. The Company determined that Casebia was considered a VIE and concluded that it is not the primary beneficiary of the VIE. As such, the Company did not consolidate Casebia's results into the consolidated financial statements. See Note 4 for further details.

Net Loss Per Share Attributable to Common Shareholders

Basic net income (loss) per share is calculated by dividing net income (loss) attributable to common shareholders by the weighted-average number of common shares outstanding during the period. Diluted net income per share is calculated by dividing the net income attributable to common shareholders by the weighted-average number of common equivalent shares outstanding for the period, including any dilutive effect from outstanding stock options and warrants using the treasury stock method.

The following table sets forth the outstanding potentially dilutive securities that have been excluded in the calculation of diluted net loss per share because to do so would be anti-dilutive (in common stock equivalent shares):

	As of December 31,		
	2018	2017	2016
Outstanding options	6,689,311	6,262,339	4,535,371
Unvested unissued restricted shares	327,342	157,515	89,367
Total	7,016,653	6,419,854	4,624,738

Subsequent Events

The Company considered the events or transactions occurring after the balance sheet date, but prior to the issuance of the consolidated financial statements, for potential recognition or disclosure in its consolidated financial statements. All significant subsequent events have been properly disclosed in the consolidated financial statements.

New Accounting Pronouncements – Recently Adopted

Revenue Recognition

As described above, the Company adopted ASC 606 on January 1, 2018 using the modified retrospective method, by recognizing the cumulative effect of initially applying ASC 606 as an adjustment to the opening balance of equity at January 1, 2018. The reported results for 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"). The Company has elected a practical expedient and applied ASC 606 only to contracts that are not completed at the date of initial application

In November 2018, The FASB amended ASC 808 and ASC 606 to clarify that certain transactions between participants in a collaborative arrangement should be accounted for under ASC 606 when the counterparty is a customer. The guidance precludes an entity from presenting consideration from a transaction in a collaborative arrangement as revenue from contracts with customers if the counterparty is not a customer for that transaction. The guidance amends ASC 808 to refer to the unit-of-account guidance in ASC 606 and requires it to be used only when assessing whether a transaction is in the scope of ASC 606. The Company early adopted the guidance in Q4 2018. The adoption of this guidance did not have a material impact on the Company's financial position and results of operations.

Financial Instrument Accounting

In January 2016, the FASB issued ASU No. 2016-01, Financial Instruments - Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities ("ASU 2016-01"). The new standard amends certain aspects of accounting and disclosure requirements of financial instruments, including the requirement that equity investments with readily determinable fair values be measured at fair value with changes in fair value recognized in the results of operations. The new standard was effective January 1, 2018. The Company adopted ASU 2016-01 in the first quarter of 2018. The adoption of this guidance did not have a material impact on the Company's financial position and results of operations.

Statement of Cash Flows

As discussed above, the Company adopted ASU 2016-18 retrospectively in the first quarter of 2018 and the change in accounting principle is reflected in the statements of cash flows years ended December 31, 2018, 2017 and 2016 accordingly. The adoption of this guidance did not have a material impact on the Company's financial position and results of operations.

Business Combinations

In January 2017, the FASB issued ASU No. 2017-01, Business Combinations (Topic 805) ("ASU 2017-01"). ASU 2017-01 clarifies whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. The purpose of the guidance is to narrow the definition of a business at it relates to recording transactions as business acquisitions or asset acquisitions. The Company adopted ASU No. 2017-01 in the first quarter of 2018. The adoption of this guidance did not have a material impact on the Company's financial position and results of operations.

Stock Compensation

In May 2017, the FASB issued ASU 2017-09, Compensation – Stock Compensation ("ASU 2017-09"): Scope Modification Accounting. The new standard is intended to reduce the diversity in practice and cost and complexity when applying the guidance in Topic 718 to a change to the terms or conditions of a share-based payment award. The Company adopted ASU No. 2017-09 in the first quarter of 2018. The adoption of this guidance did not have a material impact on the Company's financial position and results of operations.

As described above, the Company early adopted ASU 2018-07 on a prospective basis on July 1, 2018. As a result of adopting this standard, the fair value of outstanding nonemployee awards as of June 30, 2018 will no longer be remeasured each reporting period. All future expense related to these awards will be recorded based on the fair value measured as of June 30, 2018, the last period prior to the adoption of ASU 2018-07. The adoption of this guidance did not have a material impact of the Company's consolidated financial statements.

New Accounting Pronouncements – To Be Adopted In Future Periods

Leases

In February 2016, the FASB issued ASU No. 2016-02, Leases ("ASU 2016-02"), which applies to all leases and will require lessees to record most leases on the balance sheet but recognize expense in a manner similar to the current standard. In July 2018, the FASB also issued ASU No. 2018-11, Codification Improvements to Topic 842, Leases ("ASU 2018-11"), which clarifies and corrects narrow aspects of the guidance issued in ASU 2016-02 (collectively "ASC 842"). On January 1, 2019, we adopted ASC 842 using the modified-retrospective approach.

The Company has reviewed its portfolio of existing leases and current accounting policies to identify and assess the potential differences that would result from applying the requirements of the new standard. The amended guidance will result in the recognition of additional right of use assets and corresponding liabilities on its condensed consolidated balance sheets. The new standard does not have a material impact on the Company's consolidated statement of operations or cash flows. The Company has implemented appropriate changes to its controls to support lease accounting and related disclosures under the new standard.

The Company has elected the package of practical expedients permitted under the transition guidance within the new standard, which among other things, allowed us to carry forward the historical lease classification.

3. Property and Equipment, net

Property and equipment, net, consists of the following (in thousands):

	As of December 31,	
	2018	2017
Computer equipment	$ 443	$ 285
Furniture, fixtures, and other	2,453	2,104
Laboratory equipment	8,964	6,603
Leasehold improvements	13,776	13,776
Construction work in process	239	0
Total property and equipment, gross	25,875	22,768
Accumulated Depreciation	(7,375)	(3,911)
Total property and equipment, net	$ 18,500	$ 18,857

Depreciation expense for the year ended December 31, 2018, 2017, and 2016 was $3.5 million, $3.0 million, and $0.9 million, respectively.

4. Variable Interest Entities

Joint Venture with Bayer Healthcare LLC

In December 2015, the Company entered into an agreement with Bayer to create a joint venture to discover, develop and commercialize new therapeutics for genetically linked diseases, including blood disorders, blindness and heart disease. On February 12, 2016, Casebia, a limited liability partnership, was formed in the United Kingdom. In March 2016 upon consummation of the JV, Bayer and the Company each received a 50% equity interest in the entity in exchange for their contributions to the entity. The Company determined that Casebia was considered a VIE and concluded that it is not the primary beneficiary of the VIE. As such, the Company did not consolidate Casebia's results into the consolidated financial statements. See Note 9 for further details.

5. Intangible Assets

The Company's intangible assets consist of acquired intellectual property rights related to the Company's initial consolidation of TRACR in April 2014. Acquired intellectual property rights had an estimated life of 10 years. Intangible assets, net of accumulated amortization, are as follows (in thousands):

Acquired intangible asset	Cost	Accumulated Amortization	Net
As of December 31, 2018	$ 547	$ (258)	$ 289
As of December 31, 2017	$ 547	$ (203)	$ 344

The Company recorded amortization expense of $0.1 million for each of the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018 the remaining amortization period was 5.3 years. The Company has not recorded any impairment charges for the years ended December 31, 2018, 2017 and 2016. The estimated future amortization of acquired intangible assets as of December 31, 2018 is expected to be as follows (in thousands):

For the Year Ended December 31,	Amount
2019	55
2020	55
2021	55
2022	55
2023	55
Thereafter	14
Total amortization	$ 289

6. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31,	
	2018	2017
Payroll and employee-related costs	$ 7,321	$ 5,550
Research costs	$ 7,973	2,285
Licensing fees	$ 625	609
Professional fees	$ 1,848	2,176
Intellectual property costs	$ 2,193	500
Accrued property and equipment	$ 294	—
Other	$ 598	241
Total	$ 20,852	$ 11,361

7. Convertible Loans

2015 Convertible Loan Agreement with Vertex and certain existing shareholders

On October 26, 2015, the Company entered into a convertible loan agreement with Vertex and certain existing shareholders (the "Vertex Convertible Loan") under which the Company could borrow up to $40.0 million. The Vertex Convertible Loan accrued interest at 2.5% per annum and had an initial maturity date of April 26, 2016 subject to acceleration upon the occurrence of certain conditions stated in the loan agreement. On various dates between November 23 and December 7, 2015, the Company borrowed aggregate net proceeds of $38.2 million. The Vertex Convertible Loan included various embedded conversion, redemption and other features, none of which required separate accounting from the host instrument under ASC 815, *Derivatives and Hedging*. On January 29, 2016, all of the outstanding principal plus accrued interest of $0.2 million under the Vertex Convertible Loan was automatically converted into 2,859,278 Series B Preferred Shares at $9.33 per share as the result of a qualified financing that triggered conversion.

Convertible Loan with Bayer HealthCare LLC

Concurrent with the execution of the Bayer Joint Venture agreement, the Company also entered into a Convertible Loan Agreement ("Bayer Convertible Loan") with Bayer for $35.0 million. The Bayer Convertible Loan accrued interest at 2.0% per annum and matured on January 29, 2016 (the "Maturity Date"). On January 29, 2016, the Company issued the Bayer Convertible Loan in exchange for aggregate net proceeds of $35.0 million. The Bayer Convertible Loan included various embedded conversion, redemption and other features, none of which required separate accounting from the host instrument under ASC 815.

Conversion of Convertible Loans to Series B Preferred Shares

On January 29, 2016, concurrent with the issuance of the Bayer Convertible Loan, all of the outstanding principal under the $35.0 million Bayer Convertible Loan automatically converted into 2,605,330 Series B Preferred Shares at $13.43 per share. The Company determined the fair value of the Bayer Convertible Loan to be $24.5 million based on the fair value of the underlying Series B Preferred Shares that were exchanged as part of the immediate conversion. As the Bayer Convertible Loan was executed in contemplation of the joint venture agreement with Bayer, the Company evaluated the Bayer Convertible Loan as part of one multiple-element arrangement and using a relative fair value allocation allocated $27.0 million of aggregate arrangement consideration to the Bayer Convertible Loan upon issuance (See Note 9). Upon conversion, the Company accreted the Bayer Convertible Loan to its face value of $35.0 million through a charge to interest expense of $8.0 million and converted the $35.0 million to Series B Preferred Shares under the conversion model.

The receipt of $35.0 million in proceeds under the Bayer Convertible Loan in exchange for equity securities, combined with the $38.2 million in proceeds from Vertex Convertible Loan, represented a qualified financing, as defined, and triggered an automatic conversion provision of the Vertex Convertible Loan Agreement. Accordingly, on January 29, 2016, the Vertex Convertible Loan, including loans from existing shareholders, plus accrued interest also converted into 2,859,278 of Series B Preferred Shares at $13.43 per share. The Company determined the fair value of the Vertex Convertible Loan to be $26.9 million based on the fair value of the underlying Series B Preferred Shares that were exchanged as part of the conversion. Upon extinguishment, the Company recorded a gain on extinguishment of $11.5 million for the difference between the carrying value of the debt and the fair value of the Series B Preferred Shares issued to settle the debt under the general extinguishment model.

8. Commitments and Contingencies

Operating Leases

As of December 31, 2018, the Company had operating leases for office and laboratory spaces. In May 2016, the Company entered into a sublease pursuant to which it subleases in Cambridge, Massachusetts its primary office and research facility space in Cambridge, Massachusetts (the "610 Main Street Sublease"). The sublease expires in December 2026 with an option to extend the term of sublease for an additional five year period if, at the time of expiation of the initial term, the sublessor does not intend to utilize the space for itself or its affiliates. The 610 Main Street Sublease contains escalating rent clauses which require higher rent payments in future years. The lease of the Company's additional research facility space, also in Cambridge, Massachusetts, expires in February 2022. In addition, the Company rents certain offices space in Zug, Switzerland on a short-term basis. Total rental expense for the years ended December 31, 2018, 2017, and 2016 was $5.7 million, $6.9 million, and $4.2 million, respectively. The Company expenses rent, including tenant improvement allowances received by the Company, on a straight-line basis over the term of the lease, including any rent-free periods.

Future minimum payments required under the leases as of December 31, 2018, are as follows (in thousands):

Years Ended December 31,	Amount
2019	$ 6,275
2020	6,866
2021	7,072
2022	5,874
2023	5,855
Thereafter	18,639
Total minimum lease payments	$ 50,581

The amounts above are net of payment to be received under a sublease agreement, totaling $0.4 million in 2019.

Letters of Credit

As of December 31, 2018 and 2017, the Company had restricted cash of $3.2 million and $3.2 million, respectively, representing letters of credit securing the Company's obligations under certain leased facilities in Cambridge, Massachusetts at 200 Sidney Street and the 610 Main Street as well as certain credit card arrangements. The letters of credit are secured by cash held in a restricted depository account. The cash deposit is recorded in restricted cash in the accompanying consolidated balance sheet as of December 31, 2018 and 2017.

Shareholder Settlement

Under the terms of a shareholder agreement existing prior to the IPO in 2016, if a U.S. common shareholder elected to file a Qualified Electing Fund ("QEF") and notified the Company of this election, the Company was required to make advance payments to the shareholder related to their individual tax liability. In September 2016, the Company formally offered an aggregate settlement of up to $2.0 million to certain U.S common shareholders in order to release the Company from any and all obligations or claims concerning and/or arising out of the Company's status as a PFIC or a Controlled Foreign Corporation (a "CFC") for any taxable year from 2013 through 2015, including for potential lack of timely notification of the Company's PFIC status (an "Annual Information Statement") for the year ended December 31, 2015.

Following the formal settlement offer in September 2016, in the fourth quarter of 2016 the Company made payments to shareholders of $2.0 million, respectively, under the terms of the accepted settlements. The obligation to make advance payments under the shareholder agreement for tax years subsequent to 2015 terminated upon the closing of the IPO.

The Company has made available a 2018 and 2017 PFIC Annual Information Statement on its website for its shareholders.

Research Agreements

The Company has engaged several research institutions and companies to identify new delivery strategies and applications of the gene-editing technology. In association with these agreements, the Company has committed to making payments for related research and development services of $0.5 million, and $0.1 million in 2019 and 2020, respectively.

The Company is also a party to a number of research license agreements which require significant upfront payments, future royalty payments and potential milestone payments from time to time. In association with these agreements, the Company has committed to making payments of $4.7 million and 2.8 million in 2019 and 2020, respectively.

In addition, the Company is also a party to intellectual property agreements, which require maintenance and milestone payments from time to time. In association with these agreements, the Company has committed to making payments for maintenance and milestones of $0.4 million and $0.1 million in 2019 and 2020, respectively.

The Company is a party to a number of manufacturing agreements that require upfront payments for the future performance of services. In connection with these agreements, the Company has made upfront payments and recorded $2.1 million as prepaid expenses on the condensed consolidated balance sheet as of December 31, 2018. The Company will amortize the prepaid balance as services are performed.

Litigation

The Company licenses a U.S. patent application from Emmanuelle Charpentier (as described in more detail in this Annual Report on Form 10-K) that was subject to interference proceedings declared by the Patent Trial and Appeal Board ("PTAB") of the U.S. Patent and Trademark Office. Following motions by the parties and other procedural matters, the PTAB concluded in February 2017 that the declared interference should be dismissed because the claim sets of the two parties were not directed to the same patentable invention in accordance with the PTAB's two-way test for patent interferences. In April 2017, Dr. Charpentier, the regents of the University of California ("UC"), and the University of Vienna (collectively "UC") appealed the PTAB decision to the U.S. Court of Appeals for the Federal Circuit ("Federal Circuit"). In the appeal, UC asked the court to review and reverse of the PTAB's February 2017 decision, which terminated the interference without determining which inventors actually invented the use of the CRISPR/Cas9 genome editing technology in eukaryotic cells. The Federal Circuit conducted a hearing on the appeal on April 30, 2018. On September 10, 2018, the Federal Circuit affirmed the PTAB's decision to terminate the interference proceeding.

In February 2018, several parties filed oppositions in the European Patent Office to the grant of the Company's in-licensed European patent. Opposition proceedings can lead to the revocation of a patent in its entirety; the maintenance of the patent as granted, or the maintenance of a patent in amended form. Opposition proceedings typically take years to resolve, including the time taken by appeals that can be filed by any of the parties. The Company cannot guarantee the outcome of the oppositions to its in-licensed European patent, and an adverse result could preclude the Company from enforcing its rights in Europe against third parties.

On December 15, 2016, the Company entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement (the "Invention Management Agreement") with the University of California, University of Vienna, Dr. Emmanuelle Charpentier, Intellia Therapeutics, Inc. Caribou Biosciences, Inc., ERS Genomics Ltd. and TRACR Hematology Ltd. Under the Invention Management Agreement, the Company is obligated to share costs related to patent maintenance, defense and prosecution. For the years ended December 31, 2018 and 2017, the Company incurred $2.4 million and $1.2 million, respectively, in shared costs. The Company recorded accrued legal costs from the cost sharing of $1.9 million and $0.4 million as of December 31, 2018 and December 31, 2017, respectively. No expense was incurred or accrued as for the year ended December 31, 2016. The Company is unable to predict the outcome of these matters and is unable to make a meaningful estimate of the amount or range of loss, if any, that could result from an unfavorable outcome.

9. Significant Contracts

Intellectual Property Agreements

CRISPR Therapeutics AG—Charpentier License Agreement

In April 2014, the Company entered into a technology license agreement with Dr. Emmanuelle Charpentier pursuant to which the Company licensed certain intellectual property rights under joint ownership from Dr. Charpentier to develop and commercialize products for the treatment or prevention of human diseases other than hemoglobinopathies ("CRISPR—Charpentier License Agreement"). In consideration for the granting of the license, the Company paid Dr. Charpentier an upfront fee of $0.1 million and agreed to pay an immaterial annual license maintenance fee if Dr. Charpentier is not otherwise engaged in a service arrangement with the Company. During the years ended December 31, 2018, 2017 and 2016, Dr. Charpentier has been in a consulting arrangement with the Company, as such, no annual payments have been made under this provision. Dr. Charpentier is entitled to receive nominal clinical milestone payments. The Company is also obligated to pay Dr. Charpentier a low single digit percentage of sublicensing payments received under any sublicense agreement with a third party. In addition, the Company is also obligated to pay to Dr. Charpentier a low single-digit percentage royalty based on annual net sales of licensed products and licensed services by the Company and its affiliates and sublicensees.

During the years ended December 31, 2018 and 2017, the Company did not record any sublicensing fees due to Dr. Charpentier in research and development expense related to the Bayer Joint Venture Agreement. During the year ended December 31, 2016, the sublicensing fees were immaterial.

TRACR Hematology Limited—Charpentier License Agreement

In April 2014, TRACR entered into a technology license agreement ("TRACR—Charpentier License Agreement") with Dr. Emmanuelle Charpentier pursuant to which TRACR licensed certain intellectual property rights under joint ownership from Dr. Charpentier to develop and commercialize products for the treatment or prevention of human diseases related to hemoglobinopathies. In consideration for the granting of the license, Dr. Charpentier is entitled to receive nominal clinical milestone payments. TRACR is also obligated to pay Dr. Charpentier a low single digit percentage of sublicensing payments received under any sublicense agreement with a third party. In addition, TRACR is obligated to pay to Dr. Charpentier low single digit percentage royalties based on annual net sales of licensed products and licensed services by the Company and its affiliates and sublicensees.

During each of the years ended December 31, 2018, 2017, and 2016 the Company recorded an immaterial amount of sublicensing fees due to Dr. Emmanuelle Charpentier in research and development expense under the terms of the TRACR—Charpentier License Agreement that was triggered by the execution of the Vertex collaboration agreements.

Invention Management Agreement

On December 15, 2016, the Company entered into an IMA, with the University of California ("California"), the University of Vienna ("Vienna"), Dr. Charpentier, Intellia therapeutics, Inc. ("Intellia"), Caribou Biosciences, Inc. ("Caribou"), ERS Genomics Ltd., or ("ERS"), and TRACR. Under the IMA, California and Vienna retroactively consent to Dr. Charpentier's licensing of her rights to the CRISPR/Cas9 intellectual property, pursuant to the license the Company has with Dr. Charpentier, to the Company, and wholly-owned subsidiary TRACR, and ERS, in the United States and globally. The IMA also provides retroactive consent of co-owners to sublicenses granted by us, TRACR and other licensees, prospective consent to sublicenses they may grant in future, retroactive approval of prior assignments by certain 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 and with respect to certain adverse claimants of the CRISPR/Cas9 intellectual property. Unless earlier terminated by the parties, the IMA will continue in effect until the later of the last expiration date of the patents underlying the gene-editing technology, or the date on which the last underlying patent application is abandoned. Under the IMA the Company is obligated to share costs related to patent maintenance, defense and prosecution. For the years ended December 31, 2018, 2017, and 2016 the Company incurred $2.4 million, $1.2 million and $2.8 million respectively, in shared costs. The Company had accrued legal costs from the cost sharing of $1.9 million and $0.4 million as of December 31, 2018 and December 31, 2017, respectively.

Patent Assignment Agreement

In November 2014, the Company entered into a patent assignment agreement ("Patent Assignment Agreement") with Dr. Emmanuelle Charpentier, Dr. Ines Fonfara, and Vienna (collectively, the "Assignors"), pursuant to which the Company was assigned all rights, title and interest in and to certain patent rights claimed in the U.S. Patent Application No.61/905,835. In consideration for the assignment of such rights, the Assignors are entitled to receive clinical milestone payments totaling up to €0.3 million (approximately $0.4 million) in the aggregate for the first human therapeutic product. The Company is also obligated to pay to the Assignors low single digit royalties based on annual net sales of licensed products and licensed services by the Company and its affiliates and sublicensees.

During the years ended December 31, 2018 and 2017, the Company did not record any sublicensing fees due to the Assignors in research and development expense under the terms of the Patent Assignment Agreement that was triggered by the execution of the Vertex collaboration agreement and the Bayer Agreement. During the year ended December 31, 2016, the sublicensing fees were immaterial.

Collaboration Agreement with and Joint Development Agreement with Vertex Pharmaceuticals, Incorporated

Summary of Agreement

On October 26, 2015, the Company entered into a strategic collaboration, option, and license agreement (as may be amended from time to time, "Collaboration Agreement") with Vertex, focused on the use of CRISPR's gene editing technology, known as CRISPR/Cas9, to discover and develop potential new treatments aimed at the underlying genetic causes of human disease. On December 12, 2017, the Company and Vertex entered into Amendment No. 1 to the Collaboration Agreement (the "Amendment") and the Joint Development Agreement (the "JDA"). The Amendment, among other things, modified certain definitions and provisions of

the Collaboration Agreement to make them consistent with the JDA and clarified how many options are exercised (or deemed exercised) in connection with certain targets specified under the Collaboration Agreement. The Amendment also amended other provisions of the Collaboration Agreement, including the expiration terms of the Collaboration Agreement.

In connection with the Collaboration Agreement, Vertex made a nonrefundable upfront payment of $75.0 million. Under the Collaboration Agreement, Vertex will fund all of the discovery activities conducted pursuant to the agreement while retaining options to co-exclusive and exclusive licenses. In December 2017, upon execution of the JDA and Amendment, Vertex exercised its option to obtain a co-exclusive license to develop and commercialize hemoglobinopathy and beta-globin targets. As such, for potential hemoglobinopathy treatments, including treatments for sickle cell disease, the Company and Vertex will share equally all research and development costs and worldwide revenues. For other targets that Vertex elects to license, Vertex will lead all development and global commercialization activities. For each of up to four remaining targets that Vertex elects to license, the Company has the potential to receive up to $420.0 million in development, regulatory and commercial milestones and royalties on net product sale.

In connection with entering into the JDA, the Company received a $7.0 million up-front payment from Vertex and is eligible for a one-time low seven-digit milestone payment upon the dosing of the second patient in a clinical trial with the initial product candidate. The net profits and net losses, as applicable, incurred under the JDA will be shared equally between the Company and Vertex.

Accounting for the Collaboration Agreement, Amendment and JDA under ASC 606

As the overall arrangement was modified in December 2017, the Company applied the practical expedient in ASC 606-10-65-1 in identifying the satisfied and unsatisfied performance obligations, determining the transaction price and allocating the transaction price under the practical expedient in ASC 606.

The arrangement includes components of a customer-vendor relationship and a collaborative arrangement as defined under ASC 808. The Company will apply the guidance of ASC 606 by analogy to the vendor-customer performance obligations of the Collaboration Agreement and the performance obligations of the JDA subject to ASC 606 as outlined below. The Company will apply the guidance of ASC 808 to those elements in which there is a collaboration relationship in which both parties share equally in the risks and rewards of the research and development which include (i) development and commercialization services for currently identified shared products; (ii) R&D services for any follow-on products subject to the JDA; and (iii) committee participation.

The Company evaluated the Collaboration Agreement, Amendment and JDA in accordance with the provisions of ASC 606. The Company identified the following performance obligations: (i) the non-exclusive research license; (ii) four material rights representing the option for up to four exclusive licenses to develop and commercialize the collaboration targets; (iii) a combined performance obligation representing the co-exclusive research license, and a development and commercialization license to develop and commercialize hemoglobinopathies and beta-globin targets; and (iv) the performance of R&D Services.

The selling price of each performance obligation was determined based on the Company's estimated standalone selling price (the "ESSP"). The Company developed the ESSP for all the performance obligations included in the Collaboration Agreement and JDA with the objective of determining the price at which it would sell such an item if it were to be sold regularly on a standalone basis. The ESSP for material rights was determined based on the incremental discount given to Vertex based on the ESSP of the four remaining exclusive licenses and the exercise price paid at the time of exercise.

The Company developed the ESSP for the R&D Services primarily based on the nature of the services to be performed and estimates of the associated effort and cost of the services, adjusted for a reasonable profit margin that would be expected to be realized under similar contracts. The Company's ESSP for the satisfied and unsatisfied R&D Services was $19.3 million.

The Company's ESSP for each of the remaining material rights to obtain an exclusive license to develop and commercialize a single collaboration target are $45.6 million, $38.4 million, $17.3 million and $17.3 million for a total of $118.6 million. ESSPs for these items were determined based on probability and present value adjusted cash flows from the milestones payments owed for exclusive licenses outlined in the Collaboration Agreement less the price paid to exercise the material right option. ESSP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

The Company's ESSP for the co-exclusive research license and the development and commercialization licenses for of the hemoglobinopathy and beta-globin targets is $48.9 million. ESSP for this item was determined based on probability and present value adjusted cash flows from the equal sharing of projected worldwide net profit or net loss. ESSP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

The Company used a market-based approach to determine the ESSP of the non-exclusive research license of $1.0 million. The Company determined ESSP by use of comparative data, including in-licensed research agreements negotiated and executed within the Company.

As the Company has a right to consideration from Vertex in an amount that corresponds directly with the value of the Company's performance completed to date for the R&D services, thus the Company will recognize revenue related to the R&D services as invoiced, in line with the practical expedient in ASC 606-10-55-18.

The transaction price is comprised of: (i) original upfront payment of $75.0 million, (ii) an upfront payment of $7.0 million under the JDA, and (iii) $19.3 million of variable consideration associated with the R&D services. The R&D services revenue will be recognized as invoiced and specifically allocated to the R&D services performance obligation. The remaining transaction price of $82.0 million was allocated among the performance obligations using the relative selling price method as follows: (i) a non-exclusive research license: $0.5 million; (ii) a material right to discounts for exclusive licenses for up to four Collaboration Targets: $22.2 million, $18.7 million, $8.4 million and $8.4 million for a total of $57.7 million; and (iii) co-exclusive development and commercialization licenses for hemoglobinopathy and beta-globin targets identified in the JDA and co-exclusive research license for the follow-on products: $23.8 million.

The Company determined that the non-exclusive research license is symbolic intellectual property as Vertex receives value from the license through the Company's ongoing activities, as such, the revenue related to the non-exclusive research license is recognized ratably over the term of the arrangement. Upon the execution of the JDA, a co-exclusive research, development and commercialization license was granted for hemoglobinopathy and beta-globin targets. The Company determined that the revenue related to these licenses was recognized at a point in time, in which they were delivered at inception of the JDA in December 2017. As Vertex has material right in its option to obtain four additional exclusive licenses to develop and commercialize four additional collaboration targets, the Company determined that consideration allocated to these material rights would be included in the transaction price of the exclusive license and recognized at a point in time, upon the exercise of the option by Vertex or expiration.

Accounting for the Collaboration Agreement, Amendment and JDA under ASC 605

Under ASC 605, the Company evaluated the Collaboration Agreement, Amendment and JDA in accordance with the provisions of ASC 605-25. The Company's arrangement with Vertex contains the following deliverables: (i) a non-exclusive research license; (ii) an option to obtain an exclusive license for up to four Collaboration Targets; (iii) co-exclusive development and commercialization licenses for hemoglobinopathy and beta-globin targets identified in the JDA; (iv) co-exclusive research license for the follow-on products; (v) the performance of R&D Services under the Collaboration Agreement; and (vi) JRC participation under the Collaboration Agreement.

Management considered whether any of these deliverables could be considered separate units of accounting. Regarding the non-exclusive research license, the Company concluded that it does not have stand-alone value separate from the options to exercise the exclusive or the exercised co-exclusive licenses since Vertex would not benefit from acquiring a research license without the ability to obtain the license to commercialize the results of that research. As a result, the Company concluded that the research license should be combined with those options. Regarding the co-exclusive research license for the follow-on products, the Company concluded that it does not have stand-alone value separate from the exercised co-exclusive licenses under the JDCA since Vertex would not benefit from acquiring a research license without the license to commercialize the results of that research. The Company concluded the co-exclusive research license should be combined separately with each development and commercialization co-exclusive license granted under the JDA.

Regarding the R&D Services under the Collaboration Agreement, the Company concluded that there are other vendors in the market that could perform the related services. As such the Company concluded the R&D Services represent a separate unit of accounting. Regarding the JRC obligations, the Company concluded that the JRC obligations deliverable has standalone value from the option to license because the services could be performed by an outside party. As such the Company concluded the JRC obligations represent a separate unit of accounting.

As a result, management concluded that there following the modification are four units of accounting: (i) four individual combined units of accounting representing the non-exclusive research license, and the option for up to four exclusive licenses to develop and commercialize the collaboration targets; (ii) four individual combined units of accounting representing the co-exclusive research license, and a development and commercialization license to develop and commercialize hemoglobinopathies and beta-globin targets; (iii) the performance of R&D Services; and (iv) the participation in the JRC.

The Company determined that neither VSOE of selling price nor TPE of selling price is available for any of the units of accounting identified. Accordingly, the selling price of each unit of accounting was determined based on the Company's BESP. The

Company developed the BESP for all of the units of accounting included in the Collaboration Agreement and JDA with the objective of determining the price at which it would sell such an item if it were to be sold regularly on a standalone basis.

The Company developed the BESP for the R&D Services and the JRC participation primarily based on the nature of the services to be performed and estimates of the associated effort and cost of the services, adjusted for a reasonable profit margin that would be expected to be realized under similar contracts. The Company's BESP for the remaining R&D Services was $4.0 million. The Company's BESP for the JRC participation services was de minimis based on an estimate of time spent on preparation, participation, review and travel for the meetings.

The Company's BESP for the remaining four combined units of the non-exclusive research license and the options for an exclusive license to develop and commercialize a single collaboration target are $55.6 million, $48.4 million, $27.3 million and $27.3 million for a total of $158.6 million. BESPs for these items were determined based on probability and present value adjusted cash flows from the milestones payments owed for exclusive licenses outlined in the Collaboration Agreement. BESP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

The Company's BESP for the co-exclusive research license and the development and commercialization licenses for of the hemoglobinopathy and beta-globin targets is $48.9 million. BESP for this item was determined based on probability and present value adjusted cash flows from the equal sharing of project worldwide net profit or net loss. BESP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

Allocable arrangement consideration is comprised of: (i) deferred revenue of $80.0 million; (ii) an upfront payment of $7.0 million under the JDA; (iii) the estimated R&D services of $4.0 million; and (iv) payments related to the estimated exercise of options on future exclusive licenses for four targets of $40.0 million. The aggregate allocable arrangement consideration of $131.0 million was allocated among the separate units of accounting using the relative selling price method as follows: (i) four individual combined units of accounting representing the non-exclusive research license, and the option for up to four exclusive licenses to develop and commercialize the collaboration targets: $34.4 million, $30.0 million, $16.9 million and $16.9 million for a total of $98.2 million; (ii) four individual combined units of accounting representing the co-exclusive research license, and a development and commercialization license to develop and commercialize each of the hemoglobinopathy and beta-globin targets: $30.3 million; and (iii) the performance of R&D Services: $2.5 million.

Upon the execution of the JDA in December 2017, a research, development and commercialization license has been granted for hemoglobinopathy and beta-globin targets. The Company determined that these licenses were delivered at inception of the JDA and $30.3 million in revenue was recognized for this unit of accounting in December 2017.

Milestones under the Collaboration Agreement

The Company has evaluated all of the milestones that may be received in connection with the Collaboration Agreement and JDA. The first potential milestone the Company will be entitled to receive is the milestone in the JDA to receive a one-time low seven-digit milestone payment in any clinical trial in the initial shared product and is currently fully constrained. The remaining milestones are predominately related to the development and commercialization of a product resulting from the arrangement and are payable with respect to each selected exclusive license which have yet to be exercised and are not currently included in the determination of the transaction price. Each milestone is payable only once per collaboration target, regardless of the number of products directed to such collaboration target that achieve the relevant milestone event. There are nine remaining clinical development and regulatory approval milestones which may trigger proceeds of up to $90.0 million and $235.0 million, respectively, for each selected exclusive license, and two commercial milestones which may trigger proceeds of up to $75.0 million for each selected exclusive license (which, when combined with the $10.0 million due upon exercise of the exclusive option and the $10.0 million development milestone associated with an Investigational New Drug- enabling application, total $420.0 million for each selected Exclusive License), as follows:

Developmental Milestone Events

1. Initiation of the first Clinical Trial of a Product
2. Establishment of POC for a Product
3. Initiation of the first Phase 3 Clinical Trial of a Product
4. Acceptance of Approval Application by the FDA for a Product
5. Acceptance of Approval Application by the EMA for a Product
6. Acceptance of Approval Application by a Regulatory Authority in Japan for a Product
7. Marketing Approval in the US for a Product

8. Marketing Approval in the EU for a Product
9. Marketing Approval in Japan for a Product

Commercial Milestone Events

1. Annual Net Sales for Products with respect to a Collaboration Target exceed $500 million
2. Annual Net Sales for Products with respect to a Collaboration Target exceed $1.0 billion

There is uncertainty that the events to obtain the developmental milestones will be achieved given the nature of clinical development and the stage of the gene-editing technology. Upon exercise of the exclusive license options, developmental milestones will be constrained until the Company is sure that a significant revenue reversal will not occur. Commercial milestones and royalties relate predominantly to a license of intellectual property and are determined by sales or usage-based thresholds. The commercial milestones and royalties will be accounted for under the royalty recognition constraint and will be accounted for as constrained variable consideration. The Company will apply the royalty recognition constraint for each commercial milestone and will not recognize revenue for each until the subsequent sale of a licensed product (achievement of each) occurs.

Collaborative elements

The Company evaluated the Collaboration Agreement, Amendment and JDA in accordance with the provisions of ASC 808. The Company identified the following elements of ASC 808: (i) development and commercialization services for shared products; (ii) R&D services for follow-on products; and (iii) committee participation.

The Company evaluated that the nature of the arrangement and determined the arrangement is a cost/profit sharing arrangement and not a revenue arrangement. Therefore, the related impact of the cost sharing associated with research and development will be included in R&D expense. Expenses related to services performed by the Company will be classified as R&D expense. Payments received from Vertex for partial reimbursement of expenses are recorded as a reduction of R&D expense.

During the years ended December 31, 2018, 2017 and 2016, the Company recognized $0.6 million, $36.2 million and $4.0 million of revenue related to the collaboration with Vertex, respectively. During the years ended December 31, 2018, 2017 and 2016, the Company recognized research and development expense of $20.2 million, $9.9 million and $7.0 million, respectively. Research and development expense for 2018 is net of $13.8 million of reimbursements from Vertex.

As of December 31, 2018 and 2017, there was $57.8 million and $57.9 million of non-current deferred revenue related to the Collaboration Agreement, respectively. The transaction price allocated to the remaining performance obligations is $57.9 million as of December 31, 2018. The remaining performance obligations will be recognized as follows: four material rights to obtain an exclusive commercialization and development license at a point in time, upon exercise; and the non-exclusive research license ratably over/within the remaining two-and-a-half-year research term. As of December 31, 2018, the remaining amount to be recognized for the non-exclusive research license is not significant. R&D services will be recognized as invoiced under the practical expedient and are not disclosed within the remaining performance obligation balance. Reported amounts for 2018 are reflective of accounting under ASC 606 and amounts for 2017 are reflective of accounting under ASC 605 and therefore may not be comparable.

Joint Venture with Bayer Healthcare LLC

On December 19, 2015, the Company entered into an agreement with Bayer, to establish a joint venture ("Bayer Joint Venture") to focus on the research the development of new therapeutics to cure blood disorders, blindness, and congenital heart disease. On February 12, 2016, the Company and Bayer completed the formation of the joint venture entity, Casebia, a limited liability partnership formed in the United Kingdom. Bayer and the Company each received a 50% equity interest in the entity in exchange for their respective contributions to the entity. The Company contributed $0.1 million in cash and licensed its proprietary CRISPR/Cas9 gene editing technology and intellectual property for selected disease indications. Bayer contributed its protein engineering expertise and relevant disease know-how.

Under the agreement, Casebia has paid the Company $35.0 million in exchange for a worldwide, exclusive license to commercialize the Company's gene-editing technology specifically for the indications covered by the license. There are no milestone, royalties or other payments due to the Company under this aspect of the agreement. The Company determined that the contribution of the CRISRP/Cas9 technology by license to Casebia did not meet the definition of a business under ASC 805.

The Company also entered into a separate services agreement with Casebia, under which the Company agreed to provide compensated research and development services.

Concurrent with the execution of the Bayer Joint Venture agreement, the Company also issued a convertible note to Bayer BV (the "Bayer Convertible Loan") for gross proceeds of $35.0 million which was immediately converted to the Company's Series B Preferred Shares at a conversion price of $13.43 per share. Concurrent with the Company's initial public offering in October 2016, the Company issued and sold 2,500,000 common shares to Bayer BV, at the public offering price of $14.00 per share, resulting in aggregate net proceeds of $35.0 million.

As the agreements relating to the Bayer Joint Venture (including the gene-editing technology license and the research and development services) and the Bayer Convertible Loan were executed at the same time, the Company determined that the contracts should be combined and evaluated as a single arrangement. Additionally, the Company also determined that ASC 845, Nonmonetary Transactions ("ASC 845") did not apply to this arrangement given the Company's significant continuing involvement with Casebia and the amount of cash involved in the arrangement. As a result, the Company analogized to the guidance within ASC 606 regarding the allocation of arrangement consideration, however elements under transaction that were not in the scope of ASC 606 were accounted for under accounting literature based on the allocated arrangement consideration.

The Company determined the total consideration to be allocated to various elements of the transaction includes (i) the total cash payment by Casebia for the technology access fee, net of the Company's $0.1 million contribution, of $34.9 million, (ii) the fair value of the equity interest in the Joint Venture of $36.4 million, (iii) the $35.0 million received from the issuance of the Bayer Convertible Loan, and (iv) $6.3 million of estimated cash consideration to be received under the research and development service arrangement, accumulating to $112.6 million.

Under ASC 606 and ASC 605, the Company identified the following performance obligations in the combined transaction:

(i) Combined element of an exclusive, worldwide, royalty free, license to the gene-editing technology specifically for the indications designated by Casebia, and delivery of the consents of the assignors of the underlying patents to the technology to develop, manufacture, and commercialize licensed products under that license

(ii) Research and development services, and

(iii) The Company also identified the issuance of the Bayer Convertible Loan as another element to be accounted for under ASC 470, *Debt.*

For ASC 606, the Company allocated consideration to the performance obligations and other elements based on the relative proportion of their estimated standalone selling prices. The Company determined the standalone selling price of the license was $71.4 million based on the consideration paid and the fair value of the 50% interest in Casebia, which was determined utilizing discounted cash flows based on reasonable estimates and assumptions of cash flows expected from Casebia. The estimated standalone selling prices of the separate research and development services was determined to be $6.3 million and of the fair value of the Bayer Convertible Loan was determined to be $24.5 million, based on the fair value of the underlying preferred shares that were exchanged as part of the immediate conversion. Using a relative standalone selling price allocation, the Company allocated the aggregate arrangement consideration paid as follows:

(i) $79.1 million was allocated to the license and patent holder consent combined element;

(ii) $27.2 million was allocated to the Bayer Convertible Loan.

The difference between combined above amounts of $106.3 million and the total transaction price of $112.6 million is due to variable consideration of $6.3 million associated with the research and development service arrangement. The amount of the transaction price related to the research and development services ($6.3 million) will be allocated specifically to the research and development performance obligation under the right to invoice practical expedient in ASC 606-10-55-18.

The combined amount attributed to the license and patent holder consent element of $79.1 million was recognized as other income for the year ended December 31, 2016.

Under ASC 605, the Company determined the fair value of the license was $71.4 million based on the consideration paid and the fair value of the 50% interest in Casebia, which was determined utilizing discounted cash flows based on reasonable estimates and assumptions of cash flows expected from Casebia. The fair value of the separate research and development services was determined to be $6.3 million. The fair value of the Bayer Convertible Loan was determined to be $24.5 million, based on the fair value of the underlying preferred shares that were exchanged as part of the immediate conversion. Using a relative fair value allocation, the Company allocated the aggregate arrangement consideration paid as follows:

(i) $63.6 million was allocated to the license and patent holder consent combined element
(ii) $0.6 million was allocated to the future research and development services

(iii) $27.0 million was allocated to the Bayer Convertible Loan

The difference between combined above amounts of $91.2 million and the total allocable arrangement consideration of $112.6 million is due to allocable arrangement consideration associated with the $6.3 million of estimated cash consideration to be received under the research and development service arrangement and the remaining $15.0 million of the license fee paid upon the delivery of the consent from the patent holders of the Company's intellectual property.

Following delivery of the patent holders' consent, which occurred on December 17, 2016, the combined amount attributed to the license and patent holder consent element and the remaining $15.0 million license fee, which amount to $78.6 million, was recognized as other income for the year ended December 31, 2016. The Company had determined that the license and patent holder consent combined element did not meet the definition of revenue because the licensing of its technology in connection with the formation of a joint venture is not part of the Company's major ongoing or central operations.

As the amount allocated to the Bayer Convertible Loan represents an $8.0 million discount to its $35.0 million face value, the Company recognized interest expense during the twelve months ended December 31, 2017 equal to the discount. The Convertible Loan automatically converted into Series B preferred shares on its January 29, 2016 maturity date.

During 2016, the Company recorded an equity method investment of $36.5 million equal to the fair value of the Company's interest in Casebia (which was included in the allocable arrangement consideration described above). During 2016, the Company recorded unrealized equity method losses of up to the remaining amount of the $36.5 million investment. The Company has no further contractual obligations to provide cash financing to Casebia and accordingly, no additional losses have been recorded beyond the initial equity amount.

The R&D services are the only remaining performance obligations as of December 31, 2018.

At December 31, 2018 and 2017, the value of the Company's equity method investment in Casebia was zero.

Collaborative elements

The Company also participates in cost sharing activities with Casebia with respect to shared research and technology licenses with other vendors. The Company evaluated that the nature of the activity and determined the arrangement is a cost/profit sharing arrangement and not a revenue arrangement. Therefore, the related impact of the cost sharing is included in R&D expense. The Company received reimbursements of $0.9 million, $4.4 million and $0.0 million for both research and license agreements during years ended December 31, 2018, 2017 and 2016, respectively, which was recorded as a reduction of R&D expense in the income statement.

Collaboration Revenue

During the years ended December 31, 2018, 2017 and 2016, the Company recognized $2.5 million, $4.8 million, and $1.2 million of revenue, respectively, related to the collaboration with Casebia. Amounts for 2018 are reflective of accounting under ASC 606 and amounts for 2017 and 2016 are reflective of accounting under ASC 605 and therefore may not be comparable. During the years ended December 31, 2018, 2017 and 2016, the Company recognized $3.8 million, $4.5 million and $1.7 million of research and development expense, respectively, in relation to its performance under the agreement. During the years ended December 31, 2018, 2017 and 2016, the Company recognized $4.3 million, $1.8 million and $0.2 million, respectively, of stock-based compensation expense related to Casebia employees. Deferred revenue related to the Company's collaboration with Casebia was $0.0 and $0.1 million as of December 31, 2018 and 2017, respectively. Unrecognized equity method losses in excess of the Company's equity investment in Casebia was $45.3 million and $21.2 million as December 31, 2018 and 2017, respectively.

Total operating expenses of Casebia for the years ended December 31, 2018, 2017 and 2016 was $53.4 million, $36.3 million and $80.8 million, respectively. Total net loss of Casebia for the years ended December 31, 2018, 2017 and 2016, was $52.5 million, $36.2 million and $80.8 million, respectively.

Collaboration Agreement with ViaCyte, Inc.

On September 17, 2018, the Company entered into a research collaboration agreement ("ViaCyte Collaboration Agreement") with ViaCyte, Inc. ("ViaCyte") focused on the discovery, development, and commercialization of gene-edited allogeneic stem cell therapies for the treatment of diabetes. Under the terms of the ViaCyte Collaboration Agreement, the Company and ViaCyte will jointly seek to develop an immune-evasive stem cell line as a first step on the path to an allogeneic stem-cell derived product. Upon

successful completion of these studies and identification of a product candidate, the parties will jointly assume responsibility for further development and commercialization worldwide.

Upon execution of the agreement, ViaCyte was entitled to receive $15.0 million from the Company payable in two installments either in cash or in common shares at the Company's option. The agreement includes certain provisions such that in the event ViaCyte sold shares received from the Company for less than $15.0 million in combined net proceeds, the Company would owe ViaCyte the deficient amount. In the event ViaCyte sold shares received from the Company for greater than $15.0 million in combined net proceeds, ViaCyte would owe the Company the surplus amount. On September 24, 2018, the Company issued 165,636 common shares to ViaCyte which had a fair value of $7.5 million. These shares were subsequently sold for $6.9 million, resulting in a deficient amount of $0.6 million. On November 15, 2018, the Company issued 214,512 common shares to ViaCyte, which had a fair value of $8.1 million. These shares were subsequently sold for $7.5 million, resulting in a deficient amount of $0.6 million, which was paid in cash on December 18, 2018. Of the total consideration paid of $16.2 million, the Company recognized $15.0 million within research and development expense and $1.2 million within other (expense) income in the statement of operations.

At the time of the agreement, ViaCyte had the option, under certain conditions, to receive an additional $10.0 million from the Company in the form of a convertible promissory note to be issued at fair value. As of November 2018, these conditions expired and the Company is no longer required to provide ViaCyte with additional funding. The ViaCyte Collaboration Agreement may remain in force for up to six years.

10. Share Capital

The Company had 52,183,139 and 41,092,969 authorized Common Shares as of December 31, 2018 and 2017, respectively, with a par value of CHF 0.03 per share. Included in the authorized Common Shares as of December 31, 2018 is 22,341 shares of unvested restricted stock award and 307,936 treasury shares, which are legally outstanding, but are not considered outstanding for accounting purposes. The Company had conditional capital reserved for future issuance of 15,579,296 Common Shares for employee benefit plans and 4,919,700 Common Shares for debt instruments as of December 31, 2018. Under Swiss law, authorized share capital was consisted of 17,756,799 and 11,799,005 Common Shares as of December 31, 2018 and 2017, respectively. The Company had conditional capital reserved for future issuance of 12,418,591 Common Shares for employee benefit plans and 4,919,700 for debt instruments as of December 31, 2017.

Common Share Issuances

In October 2016, the Company closed the sale of 4,429,311 of our common shares in our initial public offering, or the IPO, inclusive of 429,311 common shares sold by the Company pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the offering, at a price to the public of $14.00 per share. The aggregate net proceeds received by the Company from the offering were $53.7 million, after deducting underwriting discounts and commissions and other offering expenses payable by the Company. Concurrent with the IPO, the Company issued and sold 2,500,000 common shares to Bayer BV, at the IPO price $14.00 per share, or (the "Concurrent Private Placement"), resulting in aggregate net proceeds of $35.0 million in accordance with the terms of our subscription agreement with Bayer BV. Additionally, the Company issued and subsequently reacquired the unexercised overallotment Common Shares of 170,689 at no cost.

In January 2018, the Company completed an offering of 5,750,000 shares of our common shares, which were sold at a price of $22.75 per share. This offering resulted in net proceeds of $122.6 million. In September 2018, the Company completed an offering of 4,210,526 common shares, which were sold at a price to the public of $47.50 per share. This offering resulted in net proceeds of $187.6 million. In addition, the issuance proceeds from the January and September offerings were further reduced by $3.1 million of stamp taxes, which were recorded as an offset to additional paid in capital.

In addition, in August 2018, the Company entered into an At-The-Market ("ATM") sales agreement with Jefferies LLC ("Jefferies"), under which the Company may offer and sell from time to time common shares having aggregate gross proceeds of up to $125.0 million. The Company has not yet issued or sold any securities under this sales agreement.

The Common Shares have the following characteristics:

Voting Rights

The holders of Common Shares are entitled to one vote for each Common Share held at all meetings of shareholders and written actions in lieu of meetings.

Dividends

The holders of Common Shares are entitled to receive dividends, if and when declared by the Board of Directors. As of December 31, 2018, no dividends have been declared or paid since the Company's inception.

Liquidation

The holders of the Common Shares are entitled to share ratably in the Company's assets available for distribution to shareholders in the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or upon the occurrence of a deemed liquidation event.

11. Equity-based Compensation

Option and Grant Plans

In July 2016, the shareholders approved the 2016 Share Option and Incentive Plan (the "2016 Plan") and in April 2015, the shareholders approved the 2015 option and grant plan (the "2015 Plan" collectively the "Plans"). Subsequent to the IPO, no further options shall be granted under the 2015 Plan. The Plans provide for the issuance of equity awards in the form of restricted shares, options to purchase Common Shares which may constitute incentive stock options ("ISOs") or non-statutory stock options ("NSOs"), unrestricted stock unit grants, and qualified performance and market-based awards to eligible employees, officers, directors, non-employee consultants, and other key personnel. Terms of the equity awards, including vesting requirements, are determined by the Board, subject to the provisions of the Plans. Options granted by the Company typically vest over four years and have a contractual life of ten years. The Company's Board of Directors and shareholders approved an increase in the number of common shares reserved for issuance under the Company's Amended and Restated 2016 Stock Option and Incentive Plan of 2,012,684 options in May 2017, and the Company's Board of Directors approved an additional increase to the number of common shares reserved for issuance under the Company's 2018 Stock Option and Incentive Plan of an additional 4,000,000 shares in May 2018.

During the years ended December 31, 2016 and 2015, the Company also issued outstanding Common Shares previously held by Founders and Fay Corp. to employees and non-employees as equity-based compensation ("Founder Awards"), which are subject to repurchase by the Company upon termination of the holder's service relationship with the Company as well as upon certain triggering events such as termination for cause, material breach of agreement and insolvency of the holder that generally lapse over a requisite service period of four years. All of these shares were vested as of December 31, 2018.

Equity-Based Compensation Expense

Stock-based compensation, measured at the grant date based on the fair value of the award, is typically recognized as expense ratably over the requisite service period. Stock-based compensation awards subject to performance-based vesting conditions are recognized over the requisite service period using the accelerated attribution method. The following table presents stock-based compensation expense in the Company's Consolidated Statements of Operations:

	Years Ended December 31,		
	2018	2017	2016
Research and development	$ 17,557	$ 8,800	$ 4,848
General and administrative	$ 17,428	10,073	5,844
Loss from equity method investment	$ 4,275	1,763	152
Total	$ 39,260	$ 20,636	$ 10,844

Grant- Date Fair Value

The Company estimated the fair value of each employee and non-employee stock option award on the grant date using the Black-Scholes option-pricing model based on the following assumptions:

	Years Ended December 31,		
	2018	2017	2016
Employees:			
Options granted	2,188,097	2,894,850	2,411,240
Weighted - average exercise price	$ 51.82	$ 16.92	$ 12.19
Weighted-average grant date fair value	$ 33.81	$ 10.86	$ 8.47
Assumptions:			
Weighted-average expected volatility	71.9%	72.1%	81.0%
Expected term (in years)	6.0	6.0	6.0
Weighted-average risk free interest rate	2.8%	2.0%	1.4%
Expected dividend yield	0.0%	0.0%	0.0%
Non employees:			
Options granted	21,500	104,997	215,710
Weighted- average exercise price	$ 42.75	$ 18.74	$ 19.54
Weighted- average grant date fair value	$ 34.74	$ 19.35	$ 17.38
Assumptions:			
Weighted average expected volatility	77.9%	81.5%	88.2%
Expected term (in years)	10.0	9.4	10.0
Weighted-average risk free interest rate	3.0%	2.4%	2.4%
Expected dividend yield	0.0%	0.0%	0.0%

The fair value of the restricted stock awards was determined based on the fair value of Common Stock on the grant date. Prior to the adoption of ASU 2018-07 on July 1, 2018, stock options issued to non-employees and employees of Casebia were marked to market at each reporting period. As of July 1, 2018, upon the adoption of ASU 2018-07, the fair value of outstanding nonemployee awards are no longer remeasured each reporting period and expense related to these awards was recorded based on the fair value measured as of June 30, 2018.

Share Based Payment Activity

Stock Options

The following table summarizes stock option activity for employees and non-employees during the year ended December 31, 2018 (intrinsic value in thousands):

	Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2017	6,262,339	$ 13.24	8.8	$ 64,120
Granted	2,209,597	$ 51.73		
Exercised	(946,131)	$ 10.95		
Cancelled or forfeited	(836,494)	$ 20.11		
Outstanding at December 31, 2018	6,689,311	$ 25.42	8.3	68,572
Exercisable at December 31, 2018	2,541,789	$ 15.74	7.7	$ 38,486
Vested or expected to vest at December 31, 2018 (1)	6,689,311	$ 25.42	8.3	$ 68,572

(1) This represents the number of vested stock options as of December 31, 2018 plus the unvested outstanding options at December 31, 2018 expected to vest in the future.

As of December 31, 2018, the Company expects to recognize total unrecognized compensation cost related to stock options of $83.3 million over a remaining weighted-average period of 3.0 years.

During 2018 and 2017, the Company granted options to purchase 0 and 395,000 Common Shares, respectively, subject to performance-based vesting conditions. As of December 31, 2018, options to purchase 790,598 Common Shares subject to performance-based vesting conditions were vested, as performance conditions were achieved, and there were 261,135 options to purchase Common Shares subject to performance-based vesting conditions outstanding. During 2017, the Company also granted 150,000 stock options with market-based vesting conditions in which the recipient is eligible to receive between zero and 150,000 options to purchase Common Shares at the end of a four year service period based upon achieving a specified average stock price. As of December 31, 2018, no options to purchase Common Shares subject to market-based vesting conditions were vested; however, 150,000 options were earned as the specified average stock price limits were achieved. The expense for these awards is being recognized over the requisite service period.

During the years ended December 31, 2018 and 2017, the Company modified the terms of certain options held by departing employees, resulting in $3.8 million and $2.2 million of stock-based compensation expense, respectively.

Restricted Stock

The following table summarizes restricted stock activity for employees and non-employees during the year ended December 31, 2018:

	Reflected as outstanding upon vesting	Reflected as outstanding upon grant date	Total	Weighted-Average Grant Date Fair Value
Unvested restricted common shares at December 31, 2017	157,515	208,886	366,401	$ 8.49
Granted	251,500	—	251,500	$ 44.51
Vested	(77,673)	(168,613)	(246,286)	$ 7.58
Cancelled or forfeited	(4,000)	(40,273)	(44,273)	$ 8.51
Unvested restricted common shares at December 31, 2018	327,342	—	327,342	$ 36.72

During the years ended December 31, 2018 and 2017, the total fair value of restricted stock vested was $11.3 million and $8.3 million, respectively. At December 31, 2018, total unrecognized compensation expense related to unvested restricted stock was $10.2 million which the Company expects to recognize over a remaining weighted-average period of 1.9 years.

During the year ended December 31, 2016, the Company and Fay Corp. transferred 290,400 Common Shares to a founder, 268,093 of which were subject to vesting conditions with a weighted average grant date fair value of $12.65 per share. The unvested Common Shares were subject to repurchase by the Company upon termination of the holder's service relationship with the Company as well as upon certain triggering events such as termination for cause, material breach of agreement and insolvency of the holder. The shares fully vested in 2018. During the years ended December 31, 2018, 2017 and 2016, the Company recognized expense related to the Common Shares transferred to the Founder of $0.3 million, $0.8 million and $2.6 million, respectively.

12. 401(k) Savings Plan

The Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan") in November 2016. The 401(k) Plan covers all employees who meet defined minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pretax basis. The Company contributed $0.6 million, $0.5 million and $0.1 million to the 401(k) Plan for the year ended December 31, 2018, 2017 and 2016, respectively.

13. Income Taxes

The Company is subject to U.S. federal and various state corporate income taxes as well as taxes in foreign jurisdictions for the foreign parent and where foreign subsidiaries have been established.

Net loss before taxes

For the years ended December 31, 2018, 2017 and 2016, the loss before provision for income taxes consist of the following (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Domestic	$ 5,966	$ 5,184	$ 3,322
Foreign	(170,394)	(71,792)	(26,040)
Total	$ (164,428)	$ (66,608)	$ (22,718)

The (provision for) benefit from income taxes consist of the following (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Current income taxes:			
Federal	$ (416)	$ (1,533)	$ (649)
State	(131)	(42)	11
Foreign	—	6	17
Total current income taxes	(547)	(1,569)	(621)
Deferred income taxes:			
Federal	(6)	(477)	30
State	—	297	105
Foreign	—	—	2
Total deferred income taxes	(6)	(180)	137
Total income tax provision	$ (553)	$ (1,749)	$ (484)

A reconciliation of income tax expense computed at the statutory corporate income tax rate to the effective income tax rate for the years ended December 31, 2018, 2017 and 2016 is as follows:

	Years Ended December 31,		
	2018	2017	2016
Income tax expense at statutory rate	9.3%	9.3%	10.3%
State income tax, net of federal benefit	0.7%	0.3%	1.3%
Nondeductible expenses	0.0%	0.0%	1.6%
Foreign rate differential	(0.4%)	(2.5%)	(3.3%)
Statutory to US GAAP permanent differences	1.0%	1.8%	6.6%
Stock-based compensation	1.4%	(2.9%)	(4.9%)
Research credits	1.8%	0.8%	3.1%
Change in valuation allowance	(14.1%)	(9.4%)	(16.8%)
Effective income tax rate	(0.3%)	(2.6%)	(2.1%)

The federal statutory rate reflects the Switzerland mixed company service rate.

Deferred taxes are recognized for temporary differences between the basis of assets and liabilities for financial statement and income tax purposes. The significant components of the Company's deferred tax assets are comprised of the following (in thousands):

	Years Ended December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$ 25,418	$ 9,987
Accruals and reserves	1,816	1,123
Deferred Rent	3,300	3,494
Other deferred tax assets	51	36
Stock based compensation	2,871	—
Deferred revenue	3,264	1,721
Research credit	3,322	543
Total deferred tax assets	40,042	16,904
Less valuation allowance	(36,208)	(13,041)
Net deferred tax assets	3,834	3,863
Deferred tax liabilities:		
Depreciation	(3,785)	(3,791)
Intangible assets	(49)	(59)
Other deferred tax liabilities	(22)	(31)
Total deferred tax liabilities	(3,856)	(3,881)
Long term deferred taxes	$ (22)	$ (18)

The Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. Based on the Company's history of worldwide operating losses, the Company has concluded that it is more-likely-than-not that the benefit of its U.S. and non-U.S. deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance against its net deferred tax assets in Switzerland, U.S. and in the UK for its TRACR subsidiary, as of December 31, 2018 and 2017. The valuation allowance increased by $23.2 million during 2018, which is primarily attributable to losses in Switzerland.

On December 22, 2017, the Tax Cuts and Jobs Act ("the Act") was enacted in the United States. The Act reduces the U.S. federal corporate tax rate from 35% to 21%, requires companies to pay a one-time transition tax on earnings of certain foreign subsidiaries that were previously tax deferred and creates new taxes on certain foreign sourced earnings. On December 22, 2017, the SEC staff issued Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act ("SAB 118"), which allows the recording of provisional amounts during a measurement period not to extend beyond one year of the enactment date. At December 31, 2017, the Company had assessed its provisional accounting for the tax effects of enactment of the Act, including the effects on our existing deferred tax balances and the one-time transition tax. The Company has not recorded any changes to the provisional amounts recognized as of December 31, 2017 and considers the accounting final as of December 31, 2018.

As of December 31, 2018, the Company had available non-U.S. net operating loss carryforwards of $541.1 million which begin to expire in 2020.

As of December 31, 2018, the Company has U.S. domestic federal research and development credit carryforwards of $1.9 million which expire in 2038 for federal purposes, which are net of uncertain tax positions of $0.9 million. As of December 31, 2018, the Company has U.S. domestic state research and development credit carryforwards of $1.8 million which begin to expire in 2033, which are net of uncertain tax positions of $0.7 million.

ASC 740 clarifies the accounting for uncertainty in income taxes recognized in an enterprise's financial statement by prescribing the minimum recognition threshold and measurement of a tax position taken or expected to be taken in a tax return.

As of December 31, 2018, the Company had gross unrecognized tax benefits of $1.6 million of which $1.5 million would favorably impact the effective tax rate if recognized. The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2018, 2017 and 2016, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's consolidated statements of operations and comprehensive loss.

The aggregate changes in gross unrecognized tax benefits was as follows (in thousands):

	Years Ended December 31,		
	2018	2017	2016
Balance at beginning of year	$ 354	$ 163	$ 49
Increases for tax positions taken during current period	1,212	178	134
Increases for tax positions taken in prior periods	29	13	—
Decreases for tax positions taken during current period	—	—	—
Decreases for tax positions taken in prior periods	—	—	(20)
Balance at end of year	$ 1,595	$ 354	$ 163

The Company files income tax returns in the U.S. federal jurisdiction, Massachusetts, and certain non-U.S. jurisdictions. The Company is subject to U.S. federal, Massachusetts, and non-U.S. income tax examinations by authorities for all tax years.

14. Selected Quarterly Financial Data (Unaudited)

The following table sets forth the Company's quarterly financial data for the two years ended December 31, 2018.

	2018			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Collaboration revenue	$ 1,358	$ 1,088	$ 563	$ 115
Total operating expenses	28,355	38,374	49,995	$ 45,343
Loss from operations	(26,997)	(37,286)	(49,432)	$ (45,228)
Net loss	(28,300)	(38,380)	(50,711)	$ (47,590)
Net loss attributable to common shareholders	(28,300)	(38,380)	(50,711)	$ (47,590)
Net loss per share attributable to common shareholders:				
Basic	$ (0.62)	$ (0.82)	(1.07)	$ (0.92)
Diluted	$ (0.62)	$ (0.82)	$ (1.07)	$ (0.92)
Weighted-average common shares outstanding used in net loss per share attributable to common shareholders:				
Basic	45,877,428	46,842,316	47,391,988	51,688,383
Diluted	45,877,428	46,842,316	47,391,988	51,688,383

	2017			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Collaboration revenue	$ 2,703	$ 3,582	$ 2,387	$ 32,325
Total operating expenses	23,447	24,888	25,957	$ 31,353
(Loss) income from operations	(20,744)	(21,306)	(23,570)	$ 972
Net (loss) income	(21,475)	(22,315)	(24,707)	$ 140
Net (loss) income attributable to common shareholders	(21,475)	(22,315)	(24,707)	$ 140
Net (loss) income per share attributable to common shareholders:				
Basic	$ (0.54)	$ (0.56)	$ (0.62)	$ 0.00
Diluted	$ (0.54)	$ (0.56)	$ (0.62)	$ 0.00
Weighted-average common shares outstanding used in net (loss) income per share attributable to common shareholders:				
Basic	39,725,947	39,895,938	40,088,718	40,509,897
Diluted	39,725,947	39,895,938	40,088,718	41,635,843

15. Related Party Transactions

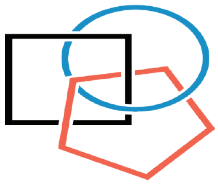
Casebia

During the years ended December 31, 2018, 2017 and 2016 the Company recognized revenue of $2.5 million, $4.8 million and $1.2 million, respectively, related to the collaboration with Casebia. During the years ended December 31, 2018, 2017 and 2016 the

Company recognized research and development expense of $3.8 million, $4.5 million and $1.7 million, respectively, related to the performance of services for Casebia. The Company and Casebia have engaged several research institutions and companies to identify new delivery strategies and applications of the gene-editing technology. Additionally, the Company and Casebia are also a party to a number of research license agreements. The Company and Casebia will share costs associated with the research and license agreements. Under both research and license agreements, the Company received reimbursements of $0.9 million, $4.4 million during 2018 and 2017, respectively. There were no reimbursements recorded during 2016. The reimbursements were recorded as a reduction of R&D expense in the income statement.

Vertex

In 2018, upon becoming owners of record of more than 10% of the voting interest of the Company, Vertex became a related party under ASC 850, *Related party disclosures.* During the year ended December 31, 2018, the Company recognized revenue of $0.6 million related to the collaboration with Vertex. During the year ended December 31, 2018, the Company recognized research and development expense of $20.2 million, related to the performance of services under the collaboration with Vertex, which is net of $13.8 million of reimbursements from Vertex.



CASEBIA

Casebia Therapeutics LLP and Subsidiary

Consolidated Financial Statements

As of and for the Years ended December 31, 2018 and 2017

Casebia Therapeutics LLP and subsidiary

Report of Independent Auditors

The Management Board and Partners

Casebia Therapeutics LLP

We have audited the accompanying consolidated financial statements of Casebia Therapeutics LLP and subsidiary, which comprise the consolidated balance sheets as of December 31, 2018 and 2017, and the related consolidated statements of operations, comprehensive loss, changes in partners' equity, and cash flows for the years then ended, and the related notes to the consolidated financial statements.

Management's Responsibility for the Financial Statements

Management is responsible for the preparation and fair presentation of these financial statements in conformity with U.S. generally accepted accounting principles; this includes the design, implementation and maintenance of internal control relevant to the preparation and fair presentation of financial statements that are free of material misstatement, whether due to fraud or error.

Auditor's Responsibility

Our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers internal control relevant to the entity's preparation and fair presentation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. Accordingly, we express no such opinion. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of significant accounting estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Opinion

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Casebia Therapeutics LLP and subsidiary at December 31, 2018 and 2017, and the consolidated results of their operations and their cash flows for the years then ended in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 25, 2019

Casebia Therapeutics LLP and subsidiary
Consolidated balance sheets

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 31,013,752	$ 26,347,434
Prepaid and other current assets	1,991,241	595,116
Due from partners	57,969	1,330,405
Total current assets	33,062,962	28,272,955
Property and equipment, net	10,434,729	9,906,893
Restricted cash	1,225,800	1,225,352
Other long-term assets	31,822	45,826
Total assets	$ 44,755,313	$ 39,451,026
Liabilities and Equity		
Current liabilities:		
Accounts payable	$ 794,386	$ 1,224,805
Accrued expenses	6,095,363	2,792,859
Due to partners	1,286,240	4,002,374
Deferred rent	675,290	590,426
Total current liabilities	8,851,279	8,610,464
Deferred rent	3,650,758	4,341,203
Total liabilities	12,502,037	12,951,667
Commitments and contingencies (see accompanying notes)		
Partners' equity:		
Partners' equity	32,253,276	26,499,359
Total partners' equity	32,253,276	26,499,359
Total liabilities and partners' equity	$ 44,755,313	$ 39,451,026

See accompanying notes to consolidated financial statements.

Casebia Therapeutics LLP and subsidiary
Consolidated statements of operations and comprehensive loss

	Years ended December 31,	
	2018	2017
Operating expenses:		
Research and development	$ 40,293,097	$ 26,607,443
General and administrative	13,107,427	9,672,302
Total operating expenses	53,400,524	36,279,745
Loss from operations	(53,400,524)	(36,279,745)
Other income:		
Interest income	886,250	57,806
Other expense	(6,340)	—
Total other income, net	879,910	57,806
Net loss and comprehensive loss	$ (52,520,614)	$ (36,221,939)

See accompanying notes to consolidated financial statements.

Casebia Therapeutics LLP and subsidiary
Consolidated statements of cash flows

	Years ended December 31,	
	2018	2017
Cash flows from operating activities:		
Net loss	$ (52,520,614)	$ (36,221,939)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	2,110,466	1,007,915
Equity-based compensation expense	4,274,531	1,729,667
Deferred rent	(605,581)	28,260
Changes in operating assets and liabilities:		
Due from partners	1,272,436	(1,330,405)
Prepaid and other current assets	(1,396,125)	(558,168)
Other long-term assets	14,004	(45,826)
Accounts payable	(323,282)	546,620
Due to partners	(2,716,134)	2,121,214
Accrued expenses	3,302,504	2,495,722
Net cash used in operating activities	(46,587,795)	(30,226,940)
Cash flows from investing activities:		
Purchases of property and equipment	(2,745,439)	(5,642,532)
Net cash used in investing activities	(2,745,439)	(5,642,532)
Cash flows from financing activities:		
Capital contributions from partners	54,000,000	60,000,000
Net cash provided by financing activities	54,000,000	60,000,000
Net increase in cash, cash equivalents and restricted cash	4,666,766	24,130,528
Cash, cash equivalents and restricted cash, beginning of period	27,572,786	3,442,258
Cash, cash equivalents and restricted cash, end of period	$ 32,239,552	$ 27,572,786
Non-cash investing activities:		
Purchases of property and equipment included in accounts payable and accrued expenses	$ 198,790	$ 305,927
Property and equipment additions acquired under tenant improvement allowance	$ —	$ 436,044

See accompanying notes to consolidated financial statements.

Casebia Therapeutics LLP and subsidiary
Consolidated statements of changes in partners' equity

	Partners' equity	Contribution receivable from partner	Total Partners' equity
Balance at December 31, 2016	$ 60,991,631	$ (60,000,000)	$ 991,631
Contributions from partners	—	60,000,000	60,000,000
Net loss	(36,221,939)	—	(36,221,939)
Equity-based compensation	1,729,667	—	1,729,667
Balance at December 31, 2017	$ 26,499,359	$ —	$ 26,499,359
Contributions from partners	54,000,000	—	54,000,000
Net loss	(52,520,614)	—	(52,520,614)
Equity-based compensation	4,274,531	—	4,274,531
Balance at December 31, 2018	$ 32,253,276	$ —	$ 32,253,276

See accompanying notes to consolidated financial statements.

Casebia Therapeutics LLP and subsidiary
Notes to consolidated financial statements

1. Organization and Operations

Organization

Casebia Therapeutics LLP (the "JV" or "Casebia") is a joint venture formed between CRISPR Therapeutics AG ("CRISPR") and Bayer HealthCare LLC ("Bayer HealthCare") in February 2016 focused on discovering, developing and commercializing CRISPR/Cas9 gene-editing therapeutics to treat the genetic causes of bleeding disorders, autoimmune disease, blindness, hearing loss, heart disease and certain metabolic diseases.

Joint Venture Agreement

The joint venture agreement between CRISPR and Bayer HealthCare (the "JV Agreement") was entered into on December 19, 2015. On February 12, 2016, CRISPR and Bayer HealthCare completed the formation of Casebia, a limited liability partnership based in the United Kingdom.

Bayer HealthCare and CRISPR each received a 50% partnership interest in the entity in exchange for their contributions to Casebia. At inception, CRISPR contributed $0.1 million in cash and licensed its proprietary CRISPR/Cas9 gene editing technology and intellectual property for selected therapeutic areas. Bayer HealthCare contributed protein engineering expertise and relevant disease know-how. Bayer HealthCare has also committed to provide up to $300.0 million in research and development funding to Casebia, subject to certain conditions. Under the joint venture agreement, CRISPR has no obligation to provide any additional funding and CRISPR's partnership interest will not be diluted from future contributions from Bayer. Casebia is a free-standing entity which has its own scientific leadership and management team. Casebia's Management Board has equal representation from Bayer HealthCare and CRISPR.

CRISPR and Bayer HealthCare also provide compensated services to Casebia through separate agreements.

Pursuant to the JV Agreement, in 2016 Casebia paid CRISPR $35.0 million in exchange for a worldwide, exclusive license to discover, develop and commercialize CRISPR's CRISPR/Cas9 technology specifically for the therapeutic areas exclusively licensed to Casebia. There are no milestone, royalty or other payments due to CRISPR under this aspect of the agreement.

The JV Agreement can be terminated by Bayer HealthCare and CRISPR upon mutual written consent. Either party may terminate the JV Agreement in the event of specified breaches by the other party or in the event the other party becomes subject to specified bankruptcy, winding up or similar circumstances. Either party may also terminate upon a change of control of the other party, as defined in the JV Agreement. Bayer HealthCare also has the right to terminate in the event (i) CRISPR is not able to maintain the intellectual property rights licensed to Casebia pursuant to the CRISPR IP Contribution Agreement or (ii) Casebia has not achieved preclinical proof of concept with a CRISPR/Cas9 product candidate in a specified period of time.

The JV Agreement may also be terminated by either party if, subsequent to the time that Bayer HealthCare has funded its entire $300.0 million commitment, Casebia is unable to obtain sufficient funding within the time specified in the JV Agreement to continue Casebia's operations for the next 18 months.

Subject to certain exceptions, in the event of a termination, all Casebia owned patents, know-how and technology will be jointly owned by CRISPR and Bayer HealthCare, with the right to sublicense. Upon termination, subject to certain exceptions, Bayer HealthCare will receive an exclusive license to Casebia CRISPR/Cas technology for all non-human therapeutic uses in cardiology, hematology and ophthalmology (the "Bayer Fields") and a non-exclusive license for human therapeutic uses. Upon such termination, CRISPR will receive an exclusive license to Casebia CRISPR/Cas technology in human therapeutic areas, other than in the Bayer Fields, and a non-exclusive license for human therapeutic uses in the Bayer Fields. Upon any termination, all rights licensed to Casebia pursuant to the CRISPR IP Contribution Agreement will terminate, except for any rights licensed to third parties or to a party who has exercised an option pursuant to the Option Agreement described below.

In connection with the establishment of the JV, Casebia, Bayer HealthCare and CRISPR entered into an Option Agreement. Pursuant to the Option Agreement, in the event the U.S. Food and Drug Administration accepts an Investigational New Drug application submitted by Casebia for any product candidate it is developing, both CRISPR and Bayer HealthCare have the right to submit a good-faith offer to enter into a license with Casebia for the exclusive right to develop, manufacture and commercialize the product candidate in certain specified fields. In addition, Casebia is allowed to receive and consider third-party offers, and both CRISPR and Bayer HealthCare can require Casebia to seek third-party offers for the applicable product candidate. The Option

Agreement sets forth the procedures the Management Board will follow when considering and voting on any offers as well as the factors to consider to determine which of the offers provides the highest value to Casebia.

Liquidity

The JV Agreement sets forth the initial 24-month budget for Casebia, which is revised by Casebia's Executive Team on a yearly basis for the following 24 months. Bayer HealthCare, subject to certain conditions, is solely responsible for providing Casebia with the necessary additional funding until the earlier of (i) its aggregate remaining commitment is fully funded, at which point all additional financing must be approved by the Management Board or (ii) the termination of the JV Agreement in accordance with its terms.

Through December 31, 2018, Bayer HealthCare has contributed $159.0 million to Casebia. In January 2019, Bayer HealthCare made an additional capital contribution in the amount of $75.0 million to Casebia.

Casebia's net loss for 2018 was $52.5 million. As of December 31, 2018, Casebia had unrestricted cash and cash equivalents of $31.0 million. Casebia believes that its cash and cash equivalents as of December 31, 2018, along with the $75.0 million capital contribution received from Bayer HealthCare in January 2019, will be sufficient to fund its current operating plan for at least the next 12 months.

2. Summary of significant accounting policies

Basis of presentation and consolidation

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of Casebia and its subsidiary. All intercompany accounts and transactions have been eliminated. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, Casebia's management evaluates its estimates, which include, but are not limited to, equity-based compensation expense and reported amounts of expenses during the reporting period. In addition, significant estimates in these consolidated financial statements have been made in connection with the calculation of the value of contributed technology and research and development expenses. Casebia bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. The consolidated statements reflect all adjustments which are of a normal recurring nature necessary for presentation. Actual results may differ from those estimates or assumptions.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. Casebia's chief operating decision maker, the chief executive officer, views Casebia's operations and manages its business in one operating segment which is the business of discovering, developing and commercializing CRISPR/Cas9 gene-editing therapeutics in the licensed therapeutic areas.

Foreign Currency Transactions

Casebia's reporting currency is the U.S. Dollar. Net foreign currency exchange transaction gains and losses resulting from the remeasurement of transactions denominated in currencies other than functional currency are included in other expense, net in the consolidated statements of operations and comprehensive loss.

Cash, cash equivalents and restricted cash

Casebia considers all highly liquid investments with maturities of 90 days or less from the purchase date to be cash equivalents. As of December 31, 2018 and 2017, Casebia held $31.0 million and $26.3 million in cash and cash equivalents, respectively, consisting of cash and money market funds. All cash was held in depository accounts and is reported at fair value.

The following table reconciles cash, cash equivalents and restricted cash reported within Casebia's consolidated balance sheets to the total of the same amounts shown in the consolidated statements of cash flows:

	As of December 31,	
	2018	2017
Cash and cash equivalents	$ 31,013,752	$ 26,347,434
Restricted cash	1,225,800	1,225,352
Total cash, cash equivalents and restricted cash shown in statement of cash flows	$ 32,239,552	$ 27,572,786

In April 2016, Casebia entered into a $1.2 million letter of credit to secure its obligations under a sublease. The letter of credit is secured by cash held in a restricted depository account.

Concentrations of Credit Risk and Off-balance Sheet Risk

Financial instruments that potentially subject Casebia to concentrations of credit risk are primarily cash and cash equivalents. Casebia's cash and cash equivalents are held in accounts with financial institutions that management believes are creditworthy. Casebia has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. Casebia has no financial instruments with off-balance sheet risk of loss.

Property and equipment

Property and equipment is stated at cost, less accumulated depreciation. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred. Upon disposal, the related cost and accumulated depreciation is removed from the accounts and any resulting gain or loss is included in the results of operations. Depreciation is recorded using the straight-line method over the estimated useful lives of the respective assets, which are as follows:

Asset	Estimated useful life
Computer equipment	3 years
Furniture, fixtures, and other	5 years
Laboratory equipment	5 years
Leasehold improvements	Shorter of useful life or remaining lease term

Research and Development Expenses

Research and development costs are comprised of costs related to employee compensation, facilities and overhead, lab supplies and materials, preclinical development, and other related costs. These costs are charged to expense as incurred.

Operating Leases

Casebia leases office and laboratory facilities under non-cancelable operating lease agreements. The lease agreements contain free or escalating rent payment provisions. Casebia recognizes rent expense under such leases on a straight-line basis over the term of the lease with the difference between the expense and the payments recorded as deferred rent on the consolidated balance sheets. Amounts received from lessors are accounted for as lease incentives, which are amortized as a reduction of rent expense over the term of the lease. Amounts received from lessees under subleases equal amounts owed under Casebia's original lease and are recognized on a straight-line basis as a reduction of rent expense over the term of the sublease. Lease renewal periods are considered on a lease-by-lease basis in determining the lease term.

Equity-based Compensation Expense

Certain employees of Casebia have been granted options to purchase CRISPR common stock. In accordance with FASB ASC Topic 323-10, Investments – Equity Method and Joint Ventures ("ASC 323-10"), CRISPR expenses the cost of the stock options granted to employees of Casebia over the award's vesting period. Concurrently, Casebia will also recognize the same cost of the stock options as an expense and capital contribution from CRISPR.

Prior to July 1, 2018, Casebia accounted for CRISPR stock options issued to Casebia employees under FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees ("ASC 505-50"). As such, the value of such options was periodically remeasured, and income or expense recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules was

recognized using the straight-line method. Casebia estimates the fair value of stock options using the Black-Scholes option pricing model.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected share price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of sufficient public market data for the trading of CRISPR's Common Shares and a lack of CRISPR-specific historical and implied volatility data, Casebia has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies have characteristics similar to CRISPR, including stage of product development and focus on the life science industry. For options granted to Casebia employees, Casebia utilizes the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. Casebia uses an assumed dividend yield of zero as CRISPR has never paid dividends and has no current plans to pay any dividends on its Common Shares.

Casebia measured CRISPR equity-based compensation awards granted to Casebia employees at fair value as the awards vested and recognized the resulting value as compensation expense at each financial reporting period.

In June 2018, the FASB issued ASU No. 2018-07, Stock Compensation ("ASU 2018-07") which provides improvements to nonemployee share-based payment accounting. ASU 2018-07 is intended to reduce the cost and complexity and to improve financial reporting for nonemployee share-based payments. The scope of ASC 718, Compensation-Stock Compensation (which currently only includes share-based payments to employees) is expanded to include share-based payments issued to nonemployees for goods or services. ASC 505-50 is superseded and consequently, the accounting for share-based payments to nonemployees and employees will be substantially aligned. Casebia early adopted this standard on a prospective basis on July 1, 2018. As a result of adopting this standard, the fair value of outstanding CRISPR stock options issued to Casebia employees as of June 30, 2018 will no longer be remeasured each reporting period. All future expense related to these awards will be recorded based on the fair value measured as of June 30, 2018, the last period prior to the adoption of ASU 2018-07. The adoption of this guidance did not have a material impact on Casebia's consolidated financial statements.

Patent Costs

Costs to secure and prosecute patent application and other legal costs related to the protection of Casebia's intellectual property are expensed as incurred and are classified as general and administrative expenses in Casebia's consolidated statements of operations.

Income taxes

Casebia is a limited liability partnership. No provision for federal income taxes is necessary in the financial statements of Casebia because, as a partnership, it is not subject to federal income tax and the tax effect of its activities accrues to the partners.

In certain circumstances, partnerships may be held to be associations taxable as corporations. The Internal Revenue Service has issued regulations specifying circumstances under current law when such a finding may be made, and management has obtained an opinion of counsel based on those regulations that the partnership is not an association taxable as a corporation. A finding that the partnership is an association taxable as a corporation could have a material adverse effect on the financial position and results of operations of the partnership.

Fair value of financial instruments

Casebia's financial instruments consist of accounts payable and accrued expenses. Casebia is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. FASB ASC Topic 820, Fair Value Measurement and Disclosures ("ASC 820"), established a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used when available. Observable inputs are inputs that market participants would use in pricing the financial instrument based on market data obtained from sources independent of Casebia. Unobservable inputs are inputs that reflect Casebia's assumptions about the inputs that market participants would use in pricing the financial instrument and are developed based on the best information available in the circumstances.

The accounting standard describes a fair value hierarchy based on three levels of inputs, of which the first two are considered observable and the last unobservable, that may be used to measure fair value, which are the following:

Level 1 — Quoted prices in active markets that are accessible at the market date for identical unrestricted assets or liabilities.

Level 2 — Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs for which all significant inputs are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

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.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by Casebia in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

Comprehensive Loss

Comprehensive loss consists of net loss and changes in equity during the period from transactions and other events and circumstances generated from non-owner sources. Casebia's net loss equals comprehensive loss for the years ended December 31, 2018 and 2017.

Subsequent Events

Casebia considers events or transactions that occur after the balance sheet date but prior to the date the financial statements are available to be issued for potential recognition or disclosure in the financial statements. Casebia has completed an evaluation of all subsequent events after the audited balance sheet date of December 31, 2018 through February 25, 2019, the date the financial statements were issued, to ensure that these financial statements include appropriate disclosure of events recognized in the financial statements as of December 31, 2018, and events which occurred subsequently but were not recognized in the financial statements.

New Accounting Pronouncements - Recently Adopted

In May 2014, the FASB issued ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606) ("ASU 2014-09"). Subsequently, the FASB also issued ASU No. 2015-14, Revenue from Contracts with Customers (Topic 606), which adjusted the effective date of ASU 2014-09; ASU No. 2016-08, Revenue from Contracts with Customers (Topic 606): Principal versus Agent Considerations (Reporting Revenue Gross versus Net), which amends the principal-versus-agent implementation guidance and illustrations in ASU 2014-09; ASU No. 2016-10, Revenue from Contracts with Customers (Topic 606): Identifying Performance Obligations and Licensing, which clarifies identifying performance obligation and licensing implementation guidance and illustrations in ASU 2014-09; and ASU No. 2016-12, Revenue from Contracts with Customers (Topic 606): Narrow-Scope Improvements and Practical Expedients, which addresses implementation issues and is intended to reduce the cost and complexity of applying the new revenue standard in ASU 2014-09 (collectively, the "Revenue ASUs").

The Revenue ASUs noted above provide an accounting standard for a single comprehensive model for use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance. The accounting standard is effective for Casebia for interim and annual periods beginning after December 15, 2018, with an option to early adopt for interim and annual periods beginning after December 15, 2016. The guidance permits two methods of adoption: retrospectively to each prior reporting period presented (the full retrospective method), or retrospectively with the cumulative effect of initially applying the guidance recognized at the date of initial application (the modified retrospective method). Casebia adopted the Revenue ASUs January 1, 2018 under the full retrospective method. The adoption of the Revenue ASUs had no effect on its consolidated financial statements as Casebia does not have any revenue generating arrangements.

In January 2017, the FASB issued ASU No. 2017-01, Business Combinations (Topic 805) ("ASU 2017-01"). ASU 2017-01 clarifies whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. The purpose of the guidance is to narrow the definition of a business at it relates recording transactions as business acquisitions or asset acquisitions.

Casebia adopted ASU 2017-01 in the first quarter of 2018. The adoption of this guidance did not have a material impact on the Casebia's consolidated financial statements.

In May 2017, the FASB issued ASU No. 2017-09, Compensation – Stock Compensation: Scope Modification Accounting ("ASU 2017-09"). This standard is intended to reduce the diversity in practice and cost and complexity when applying the guidance in Topic 718 to a change to the terms or conditions of a share-based payment award. Casebia adopted ASU No. 2017-09 in the first quarter of 2018. The adoption of this guidance did not have a material impact on Casebia's consolidated financial statements.

New Accounting Pronouncements - to be adopted in future periods

In February 2016, the FASB issued ASU No. 2016-02, Leases ("ASU 2016-02"), which applies to all leases and will require lessees to record most leases on the balance sheet but recognize expense in a manner similar to the current standard. In July 2018, the FASB also issued ASU No. 2018-11, Codification Improvements to Topic 842, Leases ("ASU 2018-11"), which clarifies and corrects narrow aspects of the guidance issued in ASU 2016-02. ASU 2016-02 and 2018-11 are effective for fiscal years beginning after December 15, 2019 and interim periods within those years, which is the year ended December 31, 2020 for Casebia. Casebia is evaluating the new guidance and anticipates that the amended guidance will result in the recognition of additional right of use assets and corresponding liabilities on its consolidated financial statements.

3. Fair Value Measurements

The fair value measurements of the Casebia's financial instruments at December 31, 2018 is summarized in the table below:

	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Balance at December 31, 2018
Assets:				
Money market funds	$ 31,013,752	$ —	$ —	$ 31,013,752
Restricted cash	1,225,800	—	—	1,225,800
Total	$ 32,239,552	$ —	$ —	$ 32,239,552

The fair value measurements of the Casebia's financial instruments at December 31, 2017 is summarized in the table below:

	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Balance at December 31, 2017
Assets:				
Money market funds	$ 26,347,434	$ —	$ —	$ 26,347,434
Restricted cash	1,225,352	—	—	1,225,352
Total	$ 27,572,786	$ —	$ —	$ 27,572,786

The carrying amounts of due from partners, due to partners, accounts payable and accrued expenses as reported in the consolidated balance sheets as of December 31, 2018 and 2017 approximate fair value due to the short-term duration of these instruments. Casebia may elect to measure financial instruments and certain other items at specified election dates in the future.

4. Prepaid and Other Current Assets

Prepaid and other current assets consist of the following:

	As of December 31,	
	2018	2017
Research costs	$ 1,535,997	$ —
Other prepaid expenses and other current assets	455,244	595,116
Total	$ 1,991,241	$ 595,116

5. Property and Equipment, net

Property and equipment, net, consists of the following:

	As of December 31,	
	2018	2017
Leasehold improvements	$ 7,796,416	$ 7,560,655
Laboratory equipment	4,770,267	2,495,309
Furniture and fixtures	735,642	676,254
Computer hardware	258,114	189,919
	13,560,439	10,922,137
Accumulated Depreciation	(3,125,710)	(1,015,244)
Property and equipment, net	$ 10,434,729	$ 9,906,893

Depreciation expense for the years ended December 31, 2018 and 2017 was $2.1 million and $1.0 million, respectively.

6. Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
	2018	2017
Payroll and employee-related costs	$ 3,083,141	$ 1,536,368
Research costs	2,406,003	935,000
Professional services	568,214	290,491
Other accrued expenses	38,005	31,000
Total	$ 6,095,363	$ 2,792,859

7. Commitments and Contingencies

Operating Leases

In August 2016, Casebia entered into an agreement with Pfizer, Inc. to sublease 32,688 square feet of office and laboratory space in Cambridge, MA. The sublease commenced in October 2016, expires in March 2024 and includes a tenant improvement allowance of $5.4 million. Casebia has the option to extend the term of the sublease by five years.

In May 2017, Casebia entered into an agreement to sublease 5,184 square feet of Casebia's office space in Cambridge, MA to Bayer HealthCare at a monthly rent per square foot equal to Casebia's monthly rent per square foot due to Pfizer. The sub-sublease was effective in May 2017 and expires in March 2024. Approximately $0.8 million of Casebia's tenant improvement allowance was allocated to improvements in the square footage occupied by Bayer HealthCare. In addition, Bayer HealthCare agreed to reimburse Casebia for approximately $1.0 million in leasehold improvements previously paid for by Casebia in excess of the tenant improvement allowance. This amount is included in Due from Partners as of December 31, 2017. Also included in Due from Partners as of December 31, 2018 and 2017, is $0.1 million and $0.3 million, respectively, of outstanding rent and operating expenses.

In April 2017, Casebia entered into an agreement with Bayer HealthCare to sublease 7,036 square feet of Bayer HealthCare's office and laboratory space in San Francisco, CA. The sublease was effective in January 2017 and expires in December 2019, with Casebia having the option to extend the term of the sublease by one year. In September 2017, Casebia entered into an amendment to increase the square footage under the sublease to 7,191, effective October 2017. In October 2018, Casebia entered into an amendment to increase the square footage under the least to 7,437, effective May 2018. In December 2018, Casebia exercised its option to extend the term of the sublease by one year to December 31, 2020.

The future minimum payments for non-cancelable leases, net of non-cancelable sublease payments, for all non-cancelable operating leases as of December 31, 2018 is as follows:

	Lease Commitments	Sublease Income	Obligations, net of sublease income
Year Ending December 31,			
2019	$ 3,055,390	$ (409,534)	$ 2,645,856
2020	3,147,147	(421,835)	2,725,312
2021	2,739,418	(434,498)	2,304,920
2022	2,821,546	(447,525)	2,374,021
2023	2,906,209	(460,953)	2,445,256
Thereafter	731,884	(116,084)	615,800
Total	$ 15,401,594	$ (2,290,429)	$ 13,111,165

From January to April 2017 Casebia occupied a portion of CRISPR's office and laboratory space on a month-to-month basis.

Total rent expense for the years ended December 31, 2018 and 2017 was $1,951,326 and $2,043,222, respectively (net of sublease income of $426,110 and $284,073, respectively).

8. Research Agreements

Seattle Children's Research Institute

In September 2017, Casebia entered into exclusive license and research collaboration agreements with Seattle Children's Research Institute ("SCRI") to explore new methods to treat and prevent autoimmune disease using CRISPR/Cas9 gene-edited regulatory T cells ("Tregs") – a type of white blood cell that controls and modulates the body's immune response. Casebia will receive worldwide rights to develop and commercialize specific intellectual property related to the collaboration. Under the terms of the collaboration agreement, Casebia will reimburse SCRI for its research costs incurred. Casebia recorded a total of $4.7 million and $0.9 million of research and development expenses under the collaboration agreement during the years ended December 31, 2018 and 2017, respectively.

In exchange for the license, in 2017 Casebia made a nonrefundable, up-front payment of $650,000 to SCRI and is also liable for annual maintenance fees of up to $350,000 per year under certain conditions for the duration of the license agreement. In addition, Casebia is obligated to make payments following the achievement of specific milestones of approximately $12.0 million. Following the first sale, if any, of a licensed product Casebia is obligated to pay royalties at a low single digit percentage of net sales of licensed products. During 2018, Casebia recorded expense of $50,000 related to the achievement of one milestone. Casebia has recorded no expense related to royalties to date under this agreement.

Other Agreements

Casebia is a party to a number of research and license agreements which require upfront payments, future royalty payments and potential milestone payments from time to time which could be significant. Casebia has recorded expense of $1.9 million and $3.9 million during the years ended December 31, 2018 and 2017, respectively, related to these agreements. In addition, Casebia has committed to making payments for related research and development services of $1.4 million in 2019, $1.4 million in 2020 and $0.1 million in 2021.

Casebia is also a party to a number of research and manufacturing agreements that require upfront payments for the future performance of services. In connection with these agreements, the Company has made upfront payments and recorded $1.6 million as prepaid expenses in the consolidated balance sheet as of December 31, 2018. The Company will amortize the prepaid balance as services are performed.

9. Equity-based Compensation

Certain employees of Casebia have been granted options to purchase CRISPR common stock. Terms of the equity awards, including vesting requirements, are determined by CRISPR's Board of Directors, subject to the provisions of CRISPR's stock option plans. Options granted by CRISPR typically vest over four years and have a contractual life of ten years. In accordance with ASC 323-

10, CRISPR expenses the cost of the stock options granted to employees of Casebia over the award's vesting period. CRISPR accounted for stock options issued to Casebia employees in accordance with ASC 505-50 through June 30, 2018, the last period prior to the adoption of ASU 2018-07. As such, the value of such options was periodically remeasured, and income or expense recognized by CRISPR over their vesting terms. All expense subsequent to the adoption of ASU 2018-07 related to CRISPR options granted to Casebia employees will be recorded based on their fair value measured as of June 30, 2018. Concurrently, Casebia will also recognize the same cost of the stock options as expense and a capital contribution from CRISPR. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method.

Equity-based Compensation Expense

Total equity-based compensation expense is recognized for stock options granted to employees and has been reported in Casebia's consolidated statement of operations as follows:

	Years ended December 31,	
	2018	2017
Research and development	$ 1,175,031	$ 660,184
General and administrative	3,099,500	1,069,483
Total	$ 4,274,531	$ 1,729,667

For equity awards that have previously been modified, any incremental increase in the fair value over the original award has been recorded as compensation expense on the date of the modification for vested awards or over the remaining service (vesting) period for unvested awards. For the year ended December 31, 2017, Casebia recorded $0.2 million of stock-based compensation expense related to the modification of stock options held by a departing employee. The incremental compensation cost is the excess of the fair value of the modified award on the date of the modification over the fair value of the original award immediately before the modification.

Stock Option Awards

The following table summarizes stock option activity for CRISPR stock options granted to employees of Casebia:

	Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2017	325,733	$ 19.01	9.1	$ 1,457,406
Granted	13,500	42.46		
Exercised	(52,570)	17.49		
Cancelled or forfeited	(6,250)	19.04		
Outstanding at December 31, 2018	280,413	$ 20.42	8.2	$ 2,473,472
Exercisable at December 31, 2018	112,322	$ 19.37	8.1	$ 1,033,872
Vested or expected to vest at December 31, 2018(1)	280,413	$ 20.42	8.2	$ 2,473,472

(1) Represents the number of vested options at December 31, 2018 plus the number of unvested options expected to vest based on the unvested options outstanding at December 31, 2018.

The fair value of options vested for the years ended December 31, 2018 and 2017 was $4.4 million and $1.6 million, respectively. The intrinsic value of options exercised for the years ended December 31, 2018 and 2017 was $1.6 million and $1.2 million, respectively. The weighted-average grant date fair values of stock options granted during the years ended December 31, 2018 and 2017 was $34.51 and $19.35, respectively.

As of December 31, 2018, the total unrecognized compensation cost related to CRISPR stock options granted to employees of Casebia was $8.3 million. The total unrecognized compensation cost will be adjusted for future forfeitures. During 2018, Casebia made an accounting policy election to account for the impact of pre-vesting forfeitures as they occur rather than applying an estimated forfeiture rate, as previously required. Adoption did not materially impact the consolidated financial statements. As of December 31, 2018, Casebia expects to recognize total unrecognized compensation cost over a remaining weighted-average period of 2.1 years.

CRISPR estimates the fair value of each stock award granted to employees of Casebia on the grant date using the Black-Scholes option-pricing model based on the following assumptions regarding the fair value of the underlying Common Shares on each measurement date:

	Years ended December 31,	
	2018	2017
Weighted average expected volatility	77.9%	81.5%
Expected term (in years)	10.0	9.4
Risk free interest rate	3.0%	2.4%
Expected dividend yield	0.0%	0.0%

10. Incentive Compensation Plans

Aspire 2.0 Plan

Certain Casebia executives are eligible to participate in Casebia's Aspire 2.0 long-term incentive plan. Beginning in 2017, on January 1 of each year, participating employees receive an award based on a percentage of their salary in virtual shares of Bayer AG. These awards vest three years after the date of grant. Upon vesting of the awards, participants receive a cash payout based on the trading price of Bayer AGs stock for the last 30 days of the vesting period, including dividends.

Casebia will revalue these awards utilizing the share price of Bayer AG common stock at each reporting period through the remaining vesting period. The revaluation may result in additional charges to expense in the future.

Total compensation expense recognized for awards granted to employees has been reported in Casebia's consolidated statement of operations as follows:

	Years ended December 31,	
	2018	2017
Research and development	$ 90,294	$ —
General and administrative	190,226	216,718
Total	$ 280,520	$ 216,718

Casebia Liquidity Event Plan

During 2017, Casebia established a Liquidity Event Plan for its employees under which participants are eligible to receive a cash award in the event Casebia experiences a change in control, as defined, or an Initial Public Offering, under certain conditions. The cash awards would be paid out over an 18-month period, or immediately if the participant's position is eliminated due to the Liquidity Event. Casebia will recognize expense for awards under this plan when a Liquidity Event is deemed probable over the requisite service period. Given the inherent uncertainty of such transactions, a Liquidity Event would not be deemed probable until the closure of a relevant transaction, therefore for the years ended December 31, 2018 and 2017, Casebia recorded no expense under the Liquidity Event Plan.

Casebia Long-term Incentive Plan

During 2017, Casebia established a Long-term Incentive Plan for its employees under which participants are eligible to receive a cash award upon the achievement of certain clinical and regulatory milestones. Casebia will recognize expense for awards under this plan as the relevant milestones are deemed probable. For the years ended December 31, 2018 and 2017, Casebia recorded no expense under the Long-term Incentive Plan.

11. Related Party Transactions

An affiliate of Bayer HealthCare has agreed to provide to Casebia certain protein engineering know-how as well as other administrative services, as detailed below. $1.2 million and $1.0 million of these expenses are included in Due to Partners in the accompanying balance sheets at December 31, 2018 and 2017, respectively.

CRISPR has also agreed to provide Casebia with certain general and administrative and research and development services, as detailed below. $0.1 million and $2.6 million of these expenses are included in Due to Partners in the accompanying balance sheet at December 31, 2018 and 2017, respectively. CRISPR and Casebia also share equally in certain in-license fees with third parties.

During 2017, Casebia employees were covered under CRISPRs medical and other benefit plans. As of December 31, 2017, $398,062 was included in Due to Partners in the accompanying balance sheet under this arrangement, representing premium and other payments made by CRISPR on behalf of Casebia.

All amounts due to Partners are due within 30 days of receipt of the respective invoices.

Total related party expenses have been reported in Casebia's consolidated statement of operations as follows:

	Years ended December 31,	
	2018	2017
Research and development:		
Bayer HealthCare and affiliates:		
Research services	$ 4,297,795	$ 3,996,384
Rent, net of sublease income	24,458	79,706
Total Bayer HealthCare and affiliates	4,322,253	4,076,090
CRISPR:		
Research services	2,303,364	4,280,233
In-license cost sharing	861,326	3,865,750
Rent	—	7,044
Total CRISPR	3,164,690	8,153,027
Total research and development	$ 7,486,943	$ 12,229,117
General and administrative:		
Bayer HealthCare and affiliates:		
Rent, net of sublease income	$ 5,464	$ 71,172
Recruiting services	—	51,517
Total Bayer HealthCare and affiliates:	5,464	122,689
CRISPR:		
Rent	—	6,289
Total CRISPR	—	6,289
Total general and administrative	$ 5,464	$ 128,978

12. Income Taxes

Casebia is a pass-through entity for federal and state income tax purposes and generally is not subject to income taxes. Instead, its earnings and losses are included in the income tax returns of the partners.

13. Employee Benefit Plan

Casebia maintains a defined contribution 401(k) plan (the "Plan") in which substantially all of its permanent employees are eligible to participate. Employee contributions are voluntary and are determined on an individual basis, limited by the maximum amounts allowable under federal tax regulations. Casebia makes matching contributions of 100% of the first 3% and 50% of the next 2% of employees' contributions to the Plan. Casebia recorded employer contribution expense of $335,538 and $168,995 for the years ended December 31, 2018 and 2017, respectively.

BOARD OF DIRECTORS

Dr. Rodger Novak
Chairman, Founder & President

Dr. Samarth Kulkarni
Chief Executive Officer

Dr. Ali Behbahani
General Partner, New Enterprise Associates

Dr. Bradley Bolzon
Managing Director, Versant Ventures

Dr. Pablo Cagnoni
Chief Executive Officer, Rubius Therapeutics

Kurt von Emster, CFA
Managing Partner, Abingworth

Dr. Simeon J. George
Chief Executive Officer, SR One

Dr. Tom Woiwode
Managing Director, Versant Ventures

EXECUTIVE COMMITTEE

Dr. Samarth Kulkarni
Chief Executive Officer

Dr. Rodger Novak
Founder & President

Dr. Tony Ho
Executive Vice President and Head of Research and Development

James R. Kasinger
General Counsel

Dr. Lawrence Klein
Chief Business Officer

Michael Tomsicek
Chief Financial Officer

CORPORATE HEADQUARTERS

Baarerstrasse 14
6300 Zug
Switzerland

US Offices

610 Main Street
Cambridge, MA 02139

UK Offices

85 Tottenham Court Road
London
W1T 4QT

TRANSFER AGENT AND REGISTRAR

American Stock Transfer & Trust Company, LLC
6201 15th Avenue
Brooklyn, NY 11219
Phone: +1.800.937.5449
www.amstock.com

INDEPENDENT AUDITORS

Ernst & Young
Basel, Switzerland
Boston, MA

LEGAL COUNSEL

VISCHER AG
Basel, Switzerland

Goodwin Procter, LLP
Boston, MA

ANNUAL GENERAL MEETING

The Annual General Meeting of Shareholders will be **June 11, 2019** at 8:00 A.M. CET at the offices of VISCHER AG, Schützengasse 1, 8001 Zurich, Switzerland

INVESTOR INFORMATION

Copies of our annual reports on Form 10-K, proxy statements, quarterly reports on Form 10-Q, and current reports on Form 8-K are available to shareholders upon request without charge. Please visit our website at www.crisprtx.com, send requests by e-mail to ir@crisprtx.com or send a written request to:

CRISPR Therapeutics, Inc., 610 Main Street, Cambridge, MA 02139, ATTN: Investor Relations

STOCK INFORMATION

Our common shares are traded on the Nasdaq Global Market under the symbol "CRSP".

FORWARD LOOKING STATEMENTS

This annual report contains “forward-looking statements” which are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. The forward-looking statements in this annual report do not constitute guarantees of future performance. Investors are cautioned that statements in this annual report that are not strictly historical statements, including, but not limited to, statements concerning: the therapeutic value, development, and commercial potential of CRISPR/Cas-9 gene editing technologies and therapies and the intellectual property protection of our technology and therapies. You are cautioned that forward-looking statements are inherently uncertain. Such forward-looking statements are subject to a number of risks and uncertainties that could cause actual results to differ materially from those anticipated, including, without limitation, the risks identified in our annual report on Form 10-K and our other filings with the Securities and Exchange Commission. We assume no obligation to update any forward- looking information contained in this annual report.

CRISPR Therapeutics AG
Baarerstrasse 14
6300 Zug
Switzerland

www.crisprtx.com