

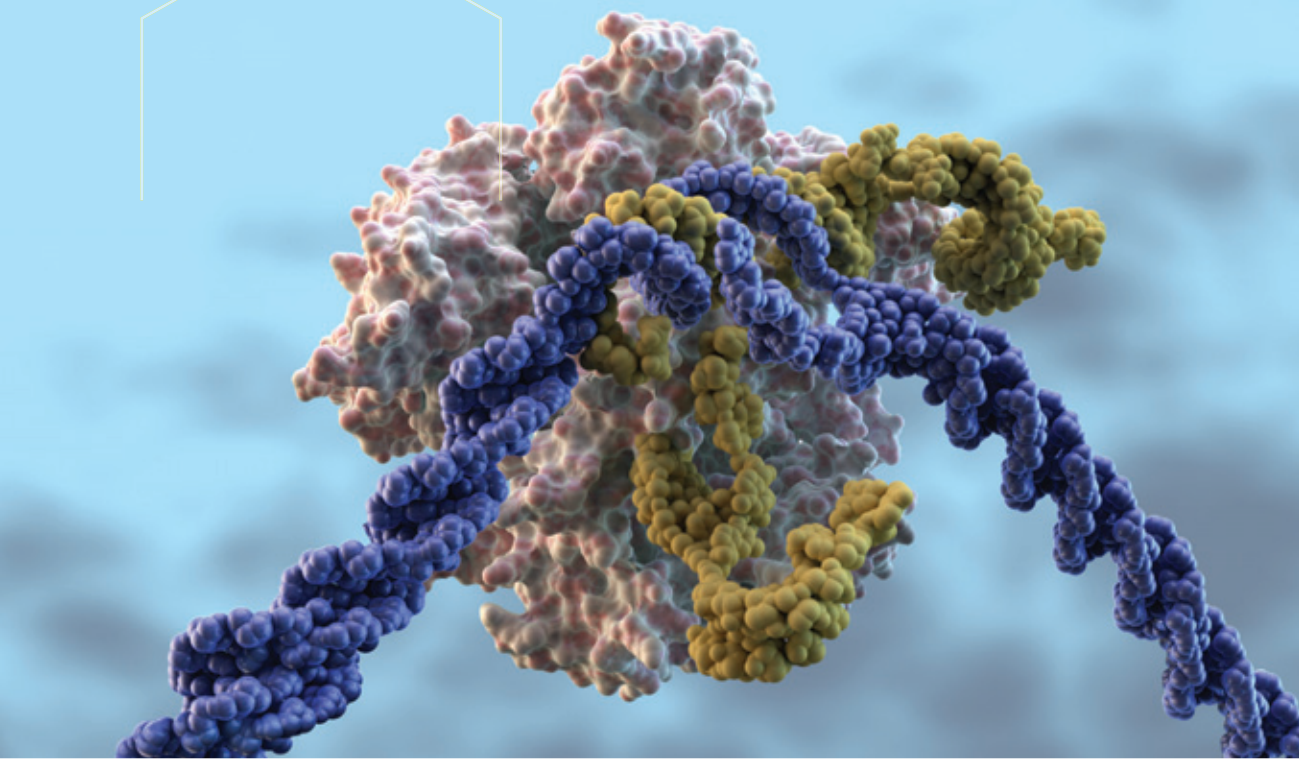


# Transformative Gene-Based Medicines

For Serious Human Diseases

2019 ANNUAL REPORT





We are rapidly translating our specific, efficient and versatile CRISPR/Cas9 gene-editing platform into therapies to treat hemoglobinopathies, cancer, diabetes and other 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, 2019

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  
(State or other jurisdiction of  
incorporation or organization)

Baarerstrasse 14

6300 Zug, Switzerland

(Address of principal executive offices)

Not Applicable  
(I.R.S. Employer  
Identification No.)

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:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Shares, nominal value CHF 0.03 par value	CRSP	The Nasdaq Global Market

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

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

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

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

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

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

Large accelerated filer  Accelerated filer

Non-accelerated filer  Smaller reporting company

Emerging growth company

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

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

The aggregate market value of the common shares held by non-affiliates of the Registrant was approximately \$2.5 billion, based on the closing price on the Nasdaq Global Market of the Registrant's common shares on June 28, 2019 (the last trading day of the Registrant's second fiscal quarter of 2019).

The number of the Registrant's common shares outstanding as of February 7, 2020 was 60,845,708.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement relating to the 2020 Annual General Meeting of Shareholders, 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, 2019, are incorporated by reference into Part III of this Report.



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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.

“CRISPR Therapeutics” is a registered trademark of CRISPR Therapeutics AG. The trademarks for “CTX001™,” “CTX110™,” “CTX120™,” and “CTX130™” are pending in the United States and the trademark for “CRISPR Therapeutics” is pending in the European Union, or EU, Switzerland and the United Kingdom. Other brands, logos, names and trademarks contained in this Annual Report on Form 10-K are the property of their respective owners. Solely for convenience, trademarks, service marks and trade names referred to in this Annual Report on Form 10-K may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights to these trademarks, service marks and trade names.

### **Special Note Regarding Forward-Looking Statements and Industry Data**

This Annual Report on Form 10-K contains “forward-looking statements” that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K are forward-looking statements. These statements are often identified by the use of words such as “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “potential,” “will,” “would” or the negative or plural of these words or similar expressions or variations, although not all forward-looking statements contain these identifying words. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the safety, efficacy and clinical progress of our and our collaborators’ various clinical programs, including CTX001, CTX110, CTX120 and CTX130;
- the status of clinical trials, development timelines and discussions with regulatory authorities related to product candidates under development by us and our collaborators;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, including our ongoing clinical trials and any planned clinical trials for CTX001, CTX110, CTX120 and CTX130, and our research and development programs;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the size and growth potential of the markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates and the success of competing therapies that are or become available;
- our intellectual property coverage and positions, including those of our licensors and third parties as well as the status and potential outcome of proceedings involving any such intellectual property;
- our ability to obtain funding for our operations and the sufficiency of our cash resources; and
- the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene-editing technologies and therapies.

Any forward-looking statements in this Annual Report on Form 10-K reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and assumptions that could cause our actual results and the timing of certain events to differ materially from future results expressed or implied by the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified herein, and those discussed in the section titled “Risk Factors,” set forth in Part I, Item 1A of this Annual Report on Form 10-K. You should not rely upon forward-looking statements as predictions of future events. Such forward-looking statements speak only as of the date of this report. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make or enter into.

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, performance or achievements may be materially different from what we expect. Except as required by law, we undertake no obligation to update any forward-looking statements to reflect events or circumstances after the date of such statements.

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.

## 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, or TDT, and severe sickle cell disease, or 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 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.

### *Hemoglobinopathies*

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 us and Vertex Pharmaceuticals Incorporated, or Vertex.

### *Beta Thalassemia*

We and Vertex are investigating CTX001 in a Phase 1/2 open-label clinical trial, CLIMB THAL-111, that is 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 the initial two patients, the trial will open for broader concurrent enrollment. CLIMB THAL-111 is designed to enroll up to 45 patients and follow patients for approximately two years after infusion. Each patient will be asked to participate in a long-term follow-up study. CTX001 has been granted Fast Track Designation by the U.S. Food and Drug Administration, or FDA, for the treatment of TDT, as well as orphan drug designation, or ODD, by the European Commission.

Enrollment is ongoing at multiple clinical trial sites globally. In the fourth quarter of 2019, we released preliminary clinical data from the first patient treated with CTX001 with TDT, and we expanded the TDT patient population for CTX001 to include beta zero/beta zero subtypes. For additional information regarding the preliminary clinical data, please see "Business—Our Lead Hemoglobinopathies Product Candidate—CTX001."

## ***Sickle Cell Disease***

We and Vertex are also investigating CTX001 in a Phase 1/2 open-label clinical trial, CLIMB SCD-121, that is 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 the initial two patients, the trial will open for broader concurrent enrollment. CLIMB SCD-121 is designed to enroll up to 45 patients and follow patients for approximately two years after infusion. Each patient will be asked to participate in a long-term follow-up study. CTX001 has been granted Fast Track Designation by the FDA for the treatment of SCD, as well as ODD by the European Commission.

Enrollment is ongoing at multiple clinical trial sites globally. In the fourth quarter of 2019, we released preliminary clinical data from the first patient treated with CTX001 with severe SCD. For additional information regarding the preliminary clinical data, please see “Business—Our Lead Hemoglobinopathies Product Candidate—CTX001.”

## ***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.

Our lead candidate, CTX110, is a healthy donor-derived gene-edited allogeneic CAR-T therapy targeting cluster of differentiation 19, or CD19, for the treatment of CD19<sup>+</sup> malignancies. We are investigating CTX110 in a Phase 1/2 clinical trial that is designed to assess the safety and efficacy of CTX110 in relapsed or refractory B-cell malignancies. The multi-center, open-label clinical trial is designed to enroll up to 95 patients and investigate several dose levels of CTX110. The trial is currently enrolling at multiple clinical trial sites globally.

Our second gene-edited allogeneic CAR-T program, CTX120, targets B-cell maturation antigen, or BCMA. We are investigating CTX120 in a Phase 1 clinical trial that is designed to assess the safety and efficacy of CTX120 in relapsed or refractory multiple myeloma. The multi-center, open-label clinical trial is designed to enroll up to 80 patients and investigate several dose levels of CTX120. The trial is currently enrolling.

Our third gene-edited CAR-T candidate, CTX130, targets CD70. CTX130 is in development for the treatment of both solid tumors, such as renal cell carcinoma, and T-cell and B-cell hematologic malignancies.

## ***Other Programs***

*Regenerative Medicine.* 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, Inc., or ViaCyte.

*In Vivo.* 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.

## ***Strategic Partnerships***

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. We maintain three broad strategic partnerships to develop gene editing-based therapeutics in specific disease areas.

*Vertex.* We established our initial collaboration agreement in 2015 with Vertex, which focused on TDT, SCD, cystic fibrosis, and select additional indications. In December 2017, we entered into a joint development and commercialization agreement with Vertex to co-develop and co-commercialize CTX001 as part of that collaboration. In June 2019, we expanded our collaboration and entered into a strategic collaboration and license agreement for the development and commercialization of products for the treatment of Duchenne muscular dystrophy and myotonic dystrophy type 1. For additional information regarding this partnership, please see “Business—Strategic Partnerships and Collaborations.”



*ViaCyte.* We entered into a research and collaboration agreement in September 2018 with ViaCyte to pursue 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. For additional information regarding this partnership, please see “Business—Strategic Partnerships and Collaborations.”

*Bayer.* In the fourth quarter of 2019, we entered into a series of transactions pursuant to which we and Bayer Healthcare LLC, or Bayer, terminated our 2015 agreement, which created the joint venture Casebia Therapeutics Limited Liability Partnership, or Casebia, 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. In connection thereto, Casebia became a wholly-owned subsidiary of ours. We and Bayer also entered into a new option agreement pursuant to which Bayer has an option to co-develop and co-commercialize two products for the diagnosis, treatment, or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders for a specified period of time, or, under certain circumstances, exclusively license such optioned products. For additional information regarding this partnership, please see “Business—Strategic Partnerships and Collaborations.”

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, or ZFNs, transcription-activator like effector nucleases, or 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. In addition, given the advantages of CRISPR/Cas systems, multiple academic groups have developed new technologies based on CRISPR/Cas9, such as base editing and prime editing. While still nascent, such new CRISPR/Cas-based technologies could have advantages over existing gene-editing technologies, including CRISPR/Cas9 technologies, in select applications.

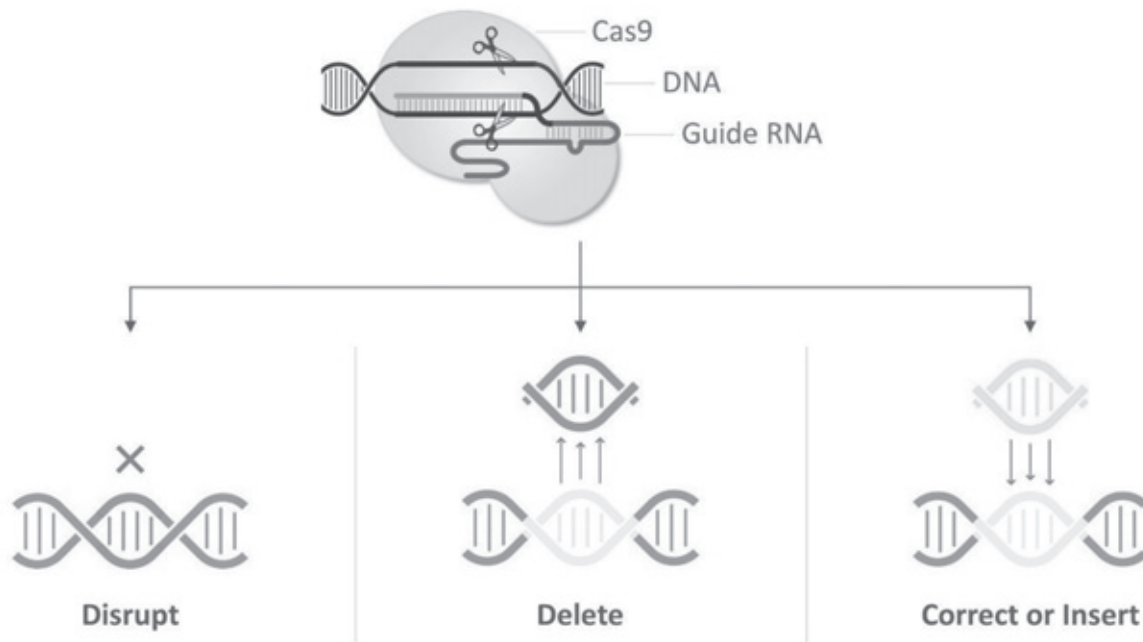
## **The CRISPR/Cas9 Technology**

CRISPR/Cas9 evolved as a naturally occurring defense mechanism that protects bacteria against viral infections. Dr. 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. 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:

## Our Pipeline

PROGRAM	RESEARCH	IND-ENABLING	CLINICAL	MARKETED	STATUS	PARTNER	STRUCTURE
<b>Hemoglobinopathies</b>							
CTX001™: β-thalassemia	□	□	□	□	Enrolling	VERTEX	Collaboration
CTX001™: Sickle cell disease (SCD)	□	□	□	□	Enrolling		Collaboration
<b>Immuno-oncology</b>							
CTX110™: Anti-CD19 allogeneic CAR-T	□	□	□	□	Enrolling		Wholly-owned
CTX120™: Anti-BCMA allogeneic CAR-T	□	□	□	□	Enrolling		Wholly-owned
CTX130™: Anti-CD70 allogeneic CAR-T	□	□	□	□			Wholly-owned
<b>Regenerative medicine</b>							
Type I diabetes mellitus	□	□	□	□		VIACTY	Collaboration
<b>In vivo approaches</b>							
Glycogen storage disease Ia (GSD Ia)	□	□	□	□			Wholly-owned
Duchenne muscular dystrophy (DMD)	□	□	□	□			License
Myotonic dystrophy type 1 (DM1)	□	□	□	□		VERTEX	Collaboration
Cystic fibrosis (CF)	□	□	□	□			License
Additional undisclosed, early stage programs subject to collaboration or license agreements with Vertex and Bayer						VERTEX	

### 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 program in hemoglobinopathies, for which we have partnered with Vertex, aims 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 EU 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. In developing countries, where chronic transfusions are not available, most patients die in early childhood. Also, a disease-modifying therapy for beta thalassemia, Reblozyl (luspatercept-aamt), recently received FDA approval.

A potentially curative therapy for this disease is allo-HSCT, but few patients elect to have this procedure given its associated morbidity and mortality. In addition, the European Medicines Agency, or EMA, recently gave a conditional marketing authorization to Zynteglo (autologous CD34<sup>+</sup> cells encoding  $\beta^{A-T87Q}$ -globin gene), a lentiviral gene therapy, for the treatment of certain patients with TDT. 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*

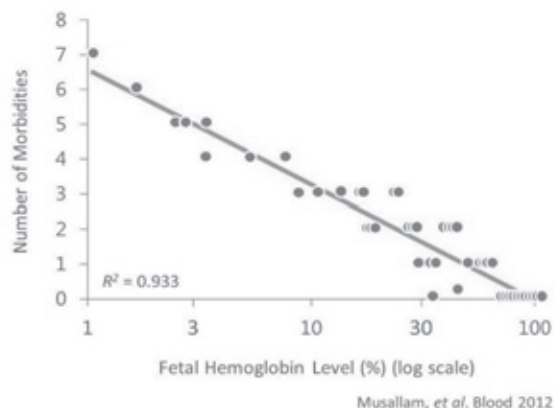
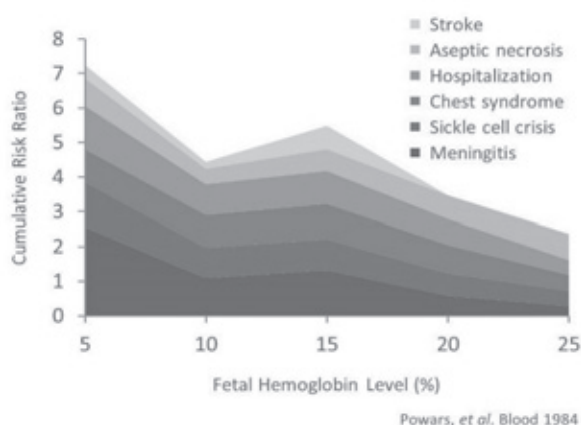
As with beta thalassemia, in regions where access to modern medical care is available, standard treatment for SCD involves chronic blood transfusions, which has the same associated risks of iron overload and toxicities associated with chelation therapy. Two disease-modifying therapies for SCD, Adakveo (crizanlizumab-tmca) and Oxbryta (voxelotor), also recently received FDA approval. Allo-HSCT is another 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

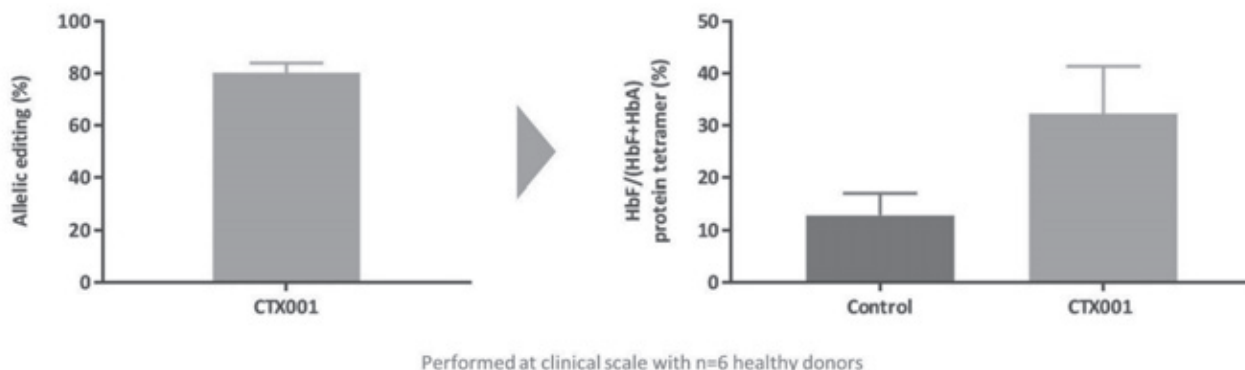
Our lead product candidate, CTX001, uses CRISPR/Cas9 to mimic the high levels of HbF that occur naturally in HPFH patients. To achieve this effect, CTX001 uses CRISPR/Cas9 to disrupt the erythroid specific enhancer of the BCL11A gene. This gene encodes the BCL11A protein, a critical factor that keeps 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.

#### Preclinical studies

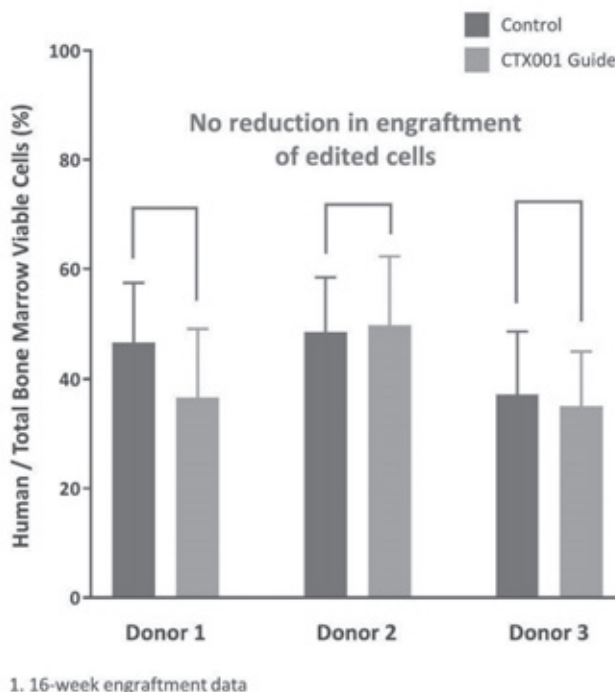
In preclinical studies using CTX001, our CRISPR/Cas9 gene-editing process demonstrated the ability to edit HSCs with approximately 80% allelic editing efficiency at clinical scale in a bulk population of cells. We observed this high editing efficiency across all stem cell subsets, including in long-term repopulating HSCs. After *in vitro* 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. 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 after *in vitro* erythroid differentiation 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.

## Editing efficiency in human CD34<sup>+</sup> cells and resulting HbF ratio after *in vitro* erythroid differentiation



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<sup>1</sup>

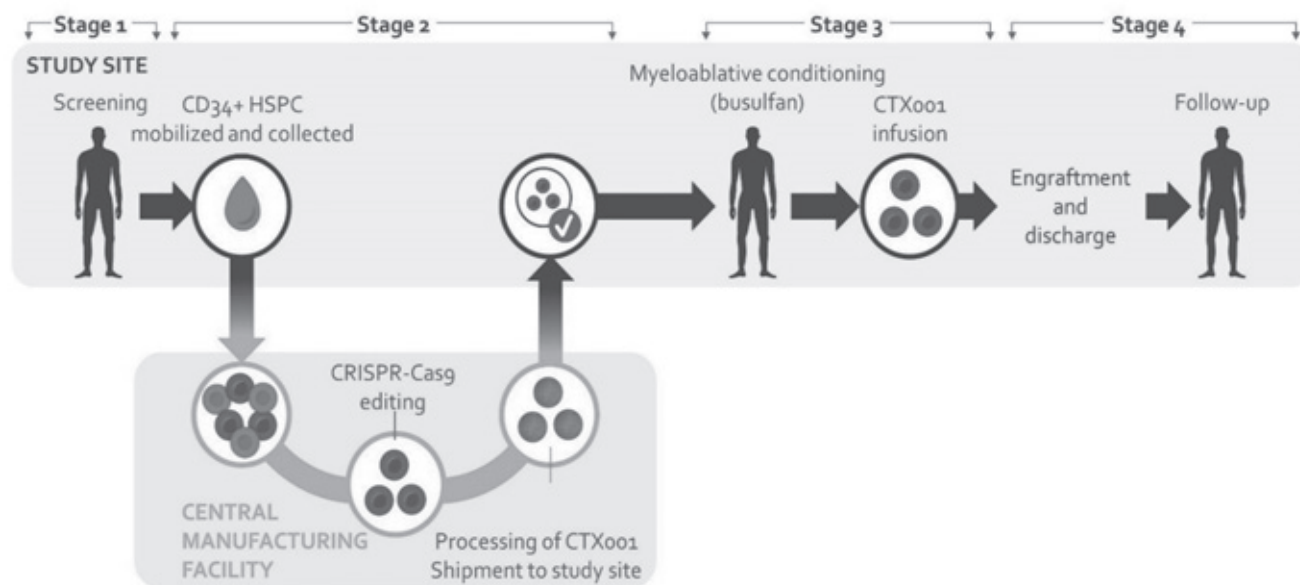


We believe our CRISPR/Cas9 gene-editing strategy may have significant advantages over other gene therapies in development for the treatment of hemoglobinopathies. For example, lentivirus-based treatments involve a random integration of one or more copies of the globin gene throughout the genome. The 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.

## Clinical Trials

We and Vertex are investigating CTX001 in two Phase 1/2 open-label clinical trials designed to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35 with TDT (CLIMB THAL-111) and severe SCD (CLIMB SCD-121), respectively. On November 19, 2019, we and Vertex announced positive safety and efficacy data from the first two patients treated with CTX001 for TDT or severe SCD in these ongoing Phase 1/2 clinical trials.

### Schematic of study procedures for the CLIMB THAL-111 and CLIMB SCD-121 Phase 1/2 trials



The patient with TDT has the  $\beta^0/IVS-I-110$  genotype and required 16.5 transfusions per year before enrolling in the clinical trial (annualized rate during the two years prior to consenting for the trial). The patient achieved successful neutrophil engraftment 33 days after CTX001 infusion and platelet engraftment 37 days after infusion. Two serious adverse events, or SAEs, occurred, neither of which the principal investigator considered related to CTX001. The SAEs were pneumonia in the presence of neutropenia and veno-occlusive liver disease attributed to busulfan conditioning, both of which subsequently resolved. This patient received a peripheral red blood cell transfusion one month following the infusion of CTX001 and from that point forward has been free from transfusions as of the nine month post-infusion data point, with total hemoglobin levels of 11.9 g/dL, 10.1 g/dL fetal hemoglobin and 99.8% F-cells (erythrocytes expressing fetal hemoglobin).

The patient with SCD experienced seven vaso-occlusive crises per year before enrolling in the clinical trial (annualized rate during the two years prior to consenting for the trial). The patient achieved neutrophil and platelet engraftment 30 days after CTX001 infusion. Three SAEs occurred, none of which the principal investigator considered related to CTX001. The SAEs were sepsis in the presence of neutropenia, cholelithiasis and abdominal pain, all of which subsequently resolved. At four months after CTX001 infusion, the patient was free of vaso-occlusive crises and had total hemoglobin levels of 11.3 g/dL, 46.6% fetal hemoglobin and 94.7% F-cells.

These trials are ongoing and patients will be followed for approximately two years following infusion.

## ***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 immune checkpoints 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.

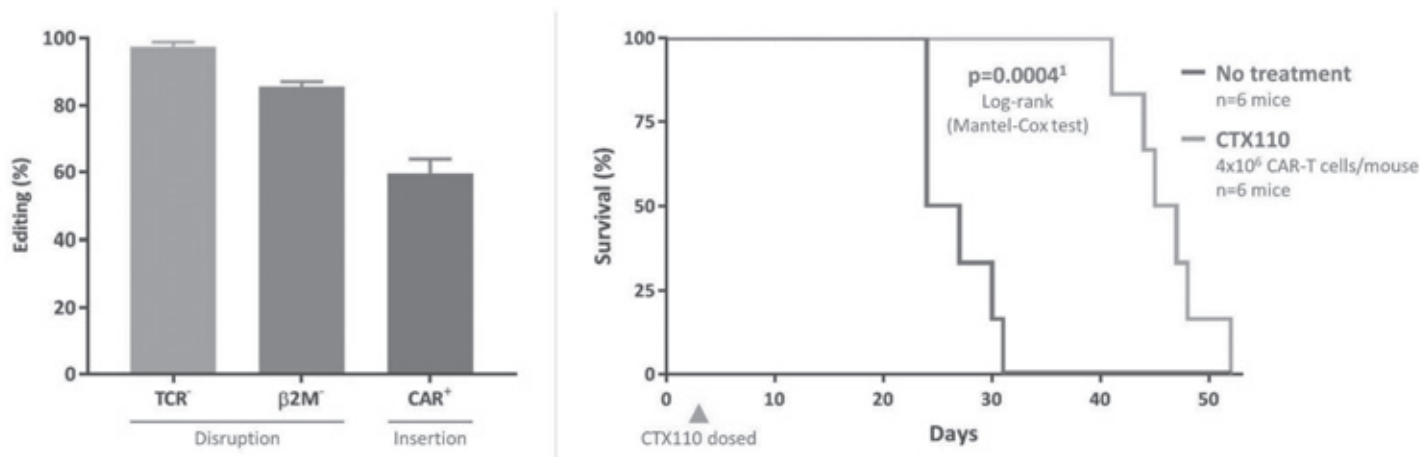
### ***Our Lead Immuno-Oncology Product Candidate—CTX110***

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 with a given 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



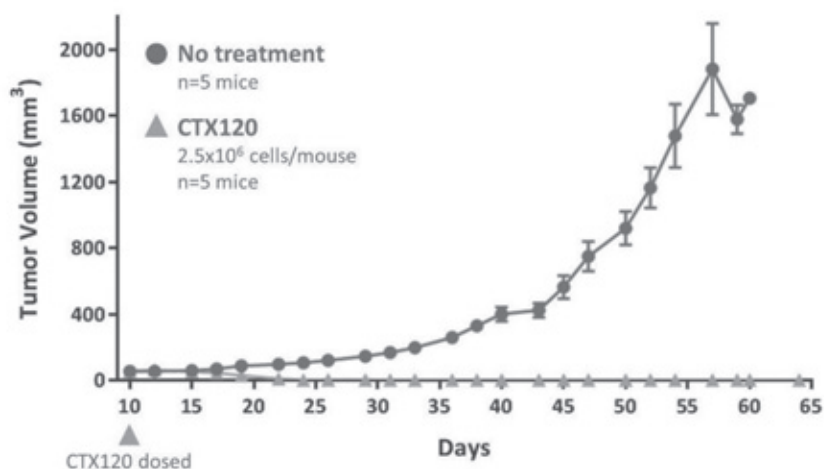
We are currently investigating CTX110 in a Phase 1/2 clinical trial that is designed to assess the safety and efficacy of CTX110 in relapsed or refractory B-cell malignancies. The multi-center, open-label clinical trial is designed to enroll up to 95 patients and investigate several dose levels of CTX110. The trial is currently enrolling at multiple clinical trial sites globally.

### CTX120

Our second gene-edited allogeneic CAR-T cell product candidate, or CTX120, is targeted towards BCMA and is in development for the treatment of relapsed or refractory 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



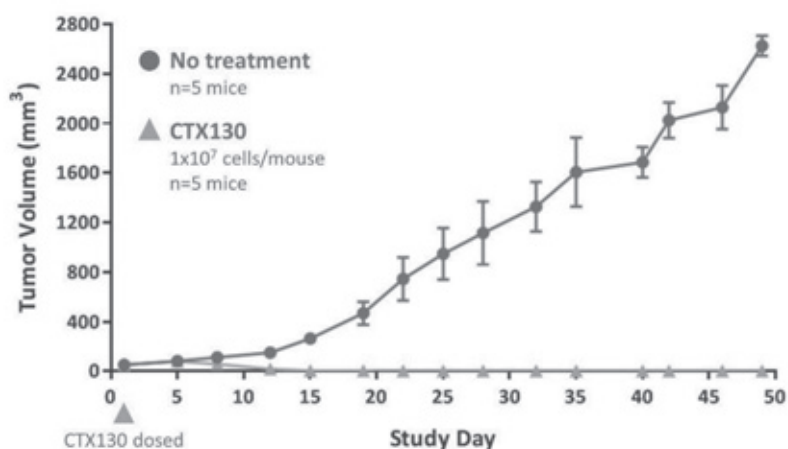
We are currently investigating CTX120 in a Phase 1 clinical trial that is designed to assess the safety and efficacy of CTX120 in relapsed or refractory multiple myeloma. The multi-center, open-label clinical trial is designed to enroll up to 80 patients and investigate several dose levels of CTX120. The trial is currently enrolling at a clinical trial site in the United States.

### CTX130

Our third gene-edited allogeneic CAR-T cell product candidate, or CTX130, is targeted towards CD70 and is in development for the treatment of both solid tumors, such as renal cell carcinoma, and T-cell and B-cell hematologic malignancies. Several cancers express CD70, including non-Hodgkin's lymphoma, certain T cell lymphomas, 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

Clinical data with islet transplants indicate that beta-cell replacement approaches may offer 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 of 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 Programs***

We are also pursuing treatments for several genetic diseases beyond the hemoglobinopathies. 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.

### ***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 regimens. 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.

## ***Vertex Partnered Programs***

We have partnered certain of our programs in other disease areas, such as Duchenne muscular dystrophy, or DMD, myotonic dystrophy type 1, or DM1, and cystic fibrosis, or CF. We have entered into collaboration agreements with respect to these three programs with Vertex, a global leader in rare diseases with extensive disease area expertise in CF. We believe that our CRISPR/Cas9 gene-editing technology is well suited to address DMD, DM1 and CF, all of which have significant patient populations with high unmet medical need.

### ***Duchenne Muscular Dystrophy (DMD)***

DMD is an X-linked recessive genetic disease caused by mutations in the dystrophin gene, which results in a lack of the dystrophin protein. Because dystrophin plays a key structural role in muscle fiber function, the absence of this protein in muscle cells leads to significant cell damage and ultimately causes muscle cell death and fibrosis. Patients with the disease experience muscle degeneration, loss of mobility and premature death. DMD is among the most prevalent severe genetic diseases, occurring in one in 3,300 male births worldwide. There are currently two approved disease-modifying therapies in the United States for the treatment of DMD, one for patients who have confirmed mutations of the dystrophin gene amenable to exon 51 skipping and one for patients who have confirmed mutations of the dystrophin gene amenable to exon 53 skipping. These mutations affect about 13% and 8% of the DMD population, respectively.

### *Myotonic dystrophy type 1 (DM1)*

DM1 is an autosomal genetic disease caused by the expansion of a CTG trinucleotide repeat in the noncoding region of the *DMPK* gene. The disease affects the skeletal and smooth muscle, as well as other organ systems, such as the eye, heart, endocrine system, and central nervous system. The clinical manifestations of DM1 span a continuum from mild to severe. Based on these phenotypes, DM1 is classified into three somewhat overlapping forms: mild, classic and congenital. Patients with mild DM1 have normal lifespans and typically develop cataracts and experience mild sustained muscle contractions, or myotonia. Those with classic DM1 tend to have muscle weakness and wasting, myotonia, cataracts and often abnormalities in cardiac conduction, and may become physically disabled and have shortened lifespans. Patients with congenital DM1 commonly have intellectual disability and typically have hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death. DM1 affects around 1 in 8,000 people worldwide. No approved therapies exist to treat the underlying disease; instead, most interventions to date aim to address specific symptoms of the disease.

### *Cystic Fibrosis (CF)*

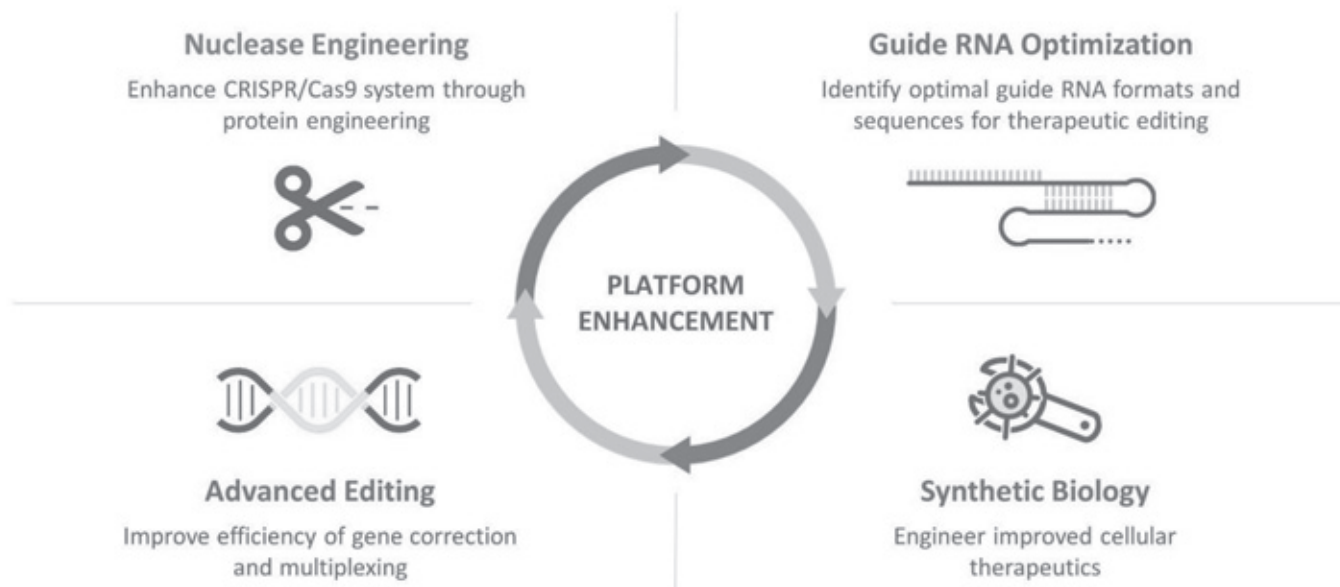
CF is a progressive disease caused by mutations in the cystic fibrosis transmembrane regulator, or CFTR, gene resulting in the loss or reduced function of the CFTR protein. Patients with CF develop thick mucus in vital organs, particularly in the lungs, pancreas and gastrointestinal tract. As a result, CF patients experience chronic severe respiratory infections, chronic lung inflammation, poor absorption of nutrients, progressive respiratory failure and early mortality. The median age of death from CF in the United States was 31 years in 2017, with most deaths resulting from respiratory failure. CF is an orphan disease that is estimated to effect more than 70,000 patients in the United States and Europe. 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.

### ***Bayer Partnered Programs***

We are also investigating programs for the diagnosis, treatment, or prevention of certain autoimmune disorders, eye disorders and hemophilia A disorders, from which Bayer has options to either co-develop and co-commercialize two products with us or, under certain circumstances, exclusively license such optioned products.

### **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 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 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. We believe 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 as 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 a selected input, such as an administered small molecule or a marker sensed on a cell surface. We believe 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 to develop gene editing-based therapeutics in specific disease areas

### *Vertex*

We have entered into a series of agreements with Vertex that contemplate certain research, development, manufacturing and commercialization activities involving various targets. Since October 2015, we have entered into a Strategic Collaboration, Option and License Agreement, as amended in 2017 and 2019, or the 2015 Collaboration Agreement; a Joint Development and Commercialization Agreement, or JDA; and a Strategic Collaboration and License Agreement, or the 2019 Collaboration Agreement.

#### *2015 Collaboration Agreement*

Pursuant to the 2015 Collaboration Agreement, we agreed to provide technology and options to obtain licenses relating to our CRISPR/Cas technology to Vertex in exchange for a \$75.0 million upfront payment. In 2015, in connection with the initial entry into the 2015 Collaboration Agreement, Vertex also made a \$30.0 million equity investment in us.

The initial focus of the 2015 Vertex collaboration was to use CRISPR/Cas9 technology to discover and develop gene-based treatments for hemoglobinopathies and cystic fibrosis. In 2017, Vertex exercised its 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. Matters relating to hemoglobinopathies targets are governed by the JDA, as summarized below. Further discovery efforts focused on a specified number of other genetic targets. Under the 2015 Collaboration Agreement, Vertex had the option to exclusively license treatments for a specified number of collaboration targets that emerged 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. We were responsible for discovery activities, and the related expenses were fully funded by Vertex.

In October 2019, Vertex exercised the remaining options granted to it under the 2015 Collaboration Agreement to exclusively in-license three additional targets for the development of gene-based treatments using CRISPR-based gene editing. The targets include the cystic fibrosis transmembrane conductance regulator gene and two undisclosed targets. Under the terms of the 2015 Collaboration Agreement, we received an upfront payment of \$30.0 million in connection with the option exercise and have the potential to receive up to \$410.0 million in development, regulatory and commercial milestones, as well as royalty payments in the single digits to low teens on net product sales for each of the three targets. The milestone and royalty payments are each subject to reduction under certain specified conditions set forth in the 2015 Collaboration Agreement. For these targets, Vertex is solely responsible for all research, development, manufacturing and global commercialization activities and Vertex received exclusive rights to develop and commercialize products related to these targets globally. The research term of the 2015 Collaboration Agreement has expired, and Vertex no longer holds rights to in-license additional targets under the 2015 Collaboration Agreement.

Either party can terminate the 2015 Collaboration Agreement upon the other party's material breach, subject to specified notice and cure provisions. Vertex also has the right to terminate the 2015 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. We may also terminate the 2015 Collaboration Agreement in the event Vertex challenges any of our patent rights.

Absent early termination, the 2015 Collaboration Agreement will continue until the expiration of the Vertex's payment obligations under the 2015 Collaboration Agreement.

#### *Joint Development Agreement*

In December 2017, we entered into the JDA with Vertex. The initial focus of the JDA is for the development of CTX001 for TDT and SCD. In connection with entering into the JDA, we received a \$7.0 million up-front payment from Vertex and subsequently received 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.* We 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 us 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.

#### *2019 Collaboration Agreement*

On June 6, 2019, we and Vertex entered the 2019 Collaboration Agreement, pursuant to which we and Vertex agreed to collaborate to develop and commercialize products for the treatment of DMD and DM1.

The 2019 Collaboration Agreement includes, among other things, provisions relating to the following:

*Governance.* We and Vertex will form a joint advisory committee to provide high-level oversight and coordination of the activities covered by the 2019 Collaboration Agreement.

*Development and Commercialization.* The 2019 Collaboration Agreement provides that Vertex will be responsible for development and commercialization activities, subject to our option, exercisable during a specified exercise period, to co-develop and co-commercialize products for the treatment of DM1.

*Financial Terms.* In connection with entering into the 2019 Collaboration Agreement, we received a \$175.0 million up-front payment from Vertex. We are eligible to receive milestone payments from Vertex of up to \$825.0 million in the aggregate, depending on the numbers and types of products that achieve pre-determined development and commercial milestones. We are also eligible to receive royalties on the sales of products ranging from the low single digits to the low double digits.

*Co-Development and Co-Commercialization Option.* If we elect to co-develop and co-commercialize products for the treatment of DM1, we would reimburse Vertex for fifty percent (50%) of the DM1 research and development costs incurred by Vertex and would be responsible for fifty percent (50%) of such costs going forward. We would receive, in lieu of further milestone or royalty payments associated with DM1 development and commercialization activities, fifty percent (50%) of all profits from sales of such products and would be responsible for fifty percent (50%) of all losses.

*Termination.* Either party may terminate the 2019 Collaboration Agreement upon the other party's material breach, subject to specified notice and cure provisions. We may also terminate the 2019 Collaboration Agreement in the event Vertex commences or participates in any action or proceeding challenging the validity or enforceability of any patent that is licensed to Vertex pursuant to the 2019 Collaboration Agreement. Vertex may also terminate the 2019 Collaboration Agreement upon our bankruptcy or insolvency, or for convenience at any time, after giving written notice.

If circumstances arise pursuant to which Vertex would have the right to terminate the 2019 Collaboration Agreement on account of an uncured material breach, Vertex may elect to keep the 2019 Collaboration Agreement in effect and reduce by a specified percentage the applicable royalties payable in respect of the product(s) that are the subject of the breach.

### ***Bayer***

In December 2015, we and Bayer entered into a joint venture agreement, or the Joint Venture Agreement, pursuant to which we and Bayer established Casebia 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. Under the Joint Venture Agreement, Bayer made available its protein engineering expertise and relevant disease know-how and we made available our proprietary CRISPR/Cas9 gene-editing technology and intellectual property. We and Bayer each held a 50% partnership interest in Casebia.

In December 2019, we, Bayer, certain subsidiaries and affiliates of us and Bayer, and Casebia entered into a series of transactions by which, among other things, Casebia became a wholly-owned subsidiary of ours; we and Bayer terminated the joint venture; and we and Bayer entered into a new option agreement, or the 2019 Option Agreement.

#### *Retirement Agreement*

On December 13, 2019, we, Bayer and Casebia entered into an agreement, or the Retirement Agreement, pursuant to which Casebia retired Bayer's outstanding partnership interests in exchange for up to \$22.0 million returned from Casebia operating cash less certain estimated interim operating expenses, subject to potential post-closing adjustments, or the Retirement.

In connection with the Retirement, our wholly-owned subsidiary simultaneously acquired a 1% partnership interest in Casebia in exchange for a capital contribution in an amount equal to 1% of the fair market value of Casebia. Accordingly, after effecting the Retirement, we and our wholly-owned subsidiary own 100% of the partnership interests in Casebia. The completion of the Retirement occurred simultaneously with the signing of the Retirement Agreement.

The Retirement Agreement contains customary representations and warranties and other customary terms for a transaction of this type.

In connection with the Retirement, the parties also entered into certain other ancillary agreements, including a joint venture termination agreement and option agreement, each summarized below.

#### *Joint Venture Termination Agreement*

In connection with entering into the Retirement Agreement, we, Bayer, certain subsidiaries and affiliates of us and Bayer, and Casebia entered into an agreement, or the Joint Venture Termination Agreement, pursuant to which we and Bayer agreed to terminate the Joint Venture Agreement consistent with the terms of such agreement.

Under the Joint Venture Termination Agreement, Casebia-owned patents, know-how and technology are now co-owned by us and Bayer, subject to certain exclusive licenses granted therein. In addition, the parties modified their rights and obligations under an amended and restated intellectual property management agreement and terminated other agreements between the parties related to the joint venture, including the CRISPR IP Contribution Agreement with Casebia, dated as of March 16, 2016, pursuant to which 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 certain fields and the existing Option Agreement, dated as of March 16, 2016, by and between us, Bayer and Casebia.

#### *2019 Option Agreement*

In connection with entering into the Retirement Agreement and the Joint Venture Termination Agreement, we and Bayer also entered into the 2019 Option Agreement pursuant to which Bayer obtained an option (exercisable during a specified exercise period defined by future events, but in no event longer than five years after the effective date of the 2019 Option Agreement) to co-develop and co-commercialize two products for the diagnosis, treatment, or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders. In the event Bayer elects to co-develop and co-commercialize a product, the parties will negotiate and enter into a co-development and co-commercialization agreement, or a Co-Commercialization Agreement, for such product, and Bayer would be responsible for 50% of the research and development costs incurred by us for such product going forward. Bayer would receive 50% of all profits from sales of such product and would be responsible for 50% of all losses.



If Bayer elects to exercise its option to co-develop and co-commercialize a product, Bayer will make a one-time \$20.0 million payment, or the Option Payment, to us that will become non-refundable once the parties execute a Co-Commercialization Agreement with respect to such optioned product. The Option Payment is payable only once with respect to the first time Bayer exercises an option under the 2019 Option Agreement.

In addition, following Bayer's exercise of its option and/or the execution of a Co-Commercialization Agreement for an optioned product, for a period beginning on the effective date of such Co-Commercialization Agreement and ending on the earlier of the three-month anniversary of such effective date or during the 90-day negotiation process of such Co-Commercialization Agreement, Bayer has a right to negotiate an exclusive license to develop and commercialize such optioned product. If Bayer exercises such right, the parties will enter into an exclusive license agreement for such optioned product on terms mutually agreeable to the parties. Further, the Option Payment paid for such optioned product would become credited against payments due under such exclusive license or any other exclusive license entered into in connection with the 2019 Option Agreement.

Either party may terminate the 2019 Option Agreement upon the other party's material breach, subject to specified notice and cure provisions. We may also terminate the 2019 Option Agreement in the event Bayer commences or participates in any action or proceeding challenging the validity or enforceability of any CRISPR patent necessary or useful for the research, development, manufacture or commercialization of a product that is the subject of the 2019 Option Agreement. Bayer may also terminate the 2019 Option Agreement upon our bankruptcy or insolvency, or for convenience at any time, after giving written notice.

### *ViaCyte*

In September 2018, we and ViaCyte entered into a research collaboration agreement, or the ViaCyte Collaboration Agreement. Pursuant to the ViaCyte Collaboration Agreement, we and ViaCyte established a research plan, or the Research Plan, for the purpose of designing and advancing allogeneic cell therapies derived from gene edited human stem cells for use in the treatment of diabetes type 1, diabetes type 2 and insulin dependent diabetes, or the Field.

For purposes of carrying out the parties' respective activities under the Research Plan, each party granted the other party a non-exclusive, royalty free, fully-paid, worldwide license to perform those activities during the research term. In addition, each party also granted the other party a non-exclusive license to research, develop, manufacture and commercialize products and product candidates for use in the Field, which is exercisable only upon the occurrence of certain termination events.

We and ViaCyte have formed a Joint Research Committee, or the JRC, comprised of three representatives from each of us and ViaCyte to review the progress of the research activities. All decisions by the JRC are made by consensus subject to specified dispute resolutions procedures. Each party to the ViaCyte Collaboration Agreement will be responsible for the costs incurred in connection with their respective activities set forth in the Research Plan. During the Research Term, neither party nor any of its affiliates may, alone or in conjunction with a third party, conduct discovery, research, development, manufacturing or commercialization activities with respect to any product which employs allogeneic cell therapy derived from gene-edited human stem cell for use in the Field.

Pursuant to the ViaCyte Collaboration Agreement, in 2018 we issued an aggregate of 380,148 shares and paid an aggregate of \$1.2 million to ViaCyte in satisfaction of our upfront payment obligations. Refer to Note 7 of the notes to our consolidated financial statements included in this Annual Report on Form 10-K for additional information.

Either party may terminate the ViaCyte Collaboration Agreement for convenience or uncured material breach, upon notice of a specified period. Either party may also terminate the ViaCyte Collaboration Agreement upon notice if the other challenges the enforceability, validity or scope of any patent rights belonging to the other party, unless the challenging party withdraws or causes the challenge to be withdrawn within a specified period. The ViaCyte Collaboration Agreement also may be terminated by either party upon the insolvency of the other party. In the event either party is acquired by specified third parties the ViaCyte Collaboration Agreement may be terminated, at the election of the non-acquired party, upon the closing of such acquisition.

### **Intellectual Property**

We strive to protect and enhance the proprietary technology, inventions, know-how 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 seeking 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. We also protect the integrity and confidentiality of our data, know-how and trade secrets by maintaining physical security of our premises and physical and electronic security of our information systems.

### *In-Licensed Intellectual Property from Dr. Charpentier*

In April 2014, pursuant to an exclusive license with Dr. 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. Charpentier.”

In addition to Dr. 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 Therapeutics, had reported that it had an exclusive license to such rights from Caribou in certain fields. We refer collectively to Dr. Charpentier, California, and Vienna as the “CVC Group”.

In January 2016, the U.S. Patent and Trademark Office, or USPTO, declared an interference (Interference No. 106,048, or ‘048 interference) between one of the pending U.S. patent applications (now issued as U.S. Patent No. 10,266,850) 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 the Broad. The interference was redeclared in March 2016 to add a U.S. patent application owned by the 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.

Following motions by the parties and other procedural matters, the PTAB concluded in February 2017 that the ‘048 interference should be terminated 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 Group 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, the CVC Group appealed the PTAB decision to the U.S. Court of Appeals for the Federal Circuit, or the Federal Circuit. In the appeal, the CVC Group 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 issued as U.S. Patent No. 10,266,850.

In June 2019, we received notification that the USPTO initiated a new interference proceeding at the PTAB, which the PTAB redeclared in August 2019 (Interference No. 106,115, or ‘115 interference). The ‘115 interference involves fourteen (14) pending U.S. patent applications co-owned by the CVC Group and thirteen (13) patents and a patent application owned by the Broad. Specifically, the PTAB declared the ‘115 interference between the CVC Group’s pending U.S. Patent Application Nos. 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; 16/136,175; 16/276,361; 16/276,365; 16/276,368; and 16/276,374, and the Broad’s U.S. Patent Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; 9,840,713, and U.S. Patent Application No. 14/704,551. This list includes the same twelve Broad patents and application that were involved in the ‘048 interference. In contrast, none of the issued U.S. patents the CVC Group owns are subject to this proceeding. The CVC Group’s inventions that are the subject of the ‘115 interference were first filed with the USPTO in May of 2012, while the Broad filed its first application seven months later in December of 2012. However, the 14 CVC Group patent applications that are involved in the current interference are continuing patent applications that were filed in 2018 and claim priority to the CVC Group’s original 2012 filing, while the Broad’s involved patents and patent application were filed between 2013 and 2015. Because the PTAB accorded neither party the benefit of any of its first filing dates, but instead accorded only the benefit of the actual filing dates of the involved patents and patent applications, the CVC Group was by default named the Junior Party. Both parties have filed motions requesting benefit of their earliest priority dates (the CVC Group in May 2012 and the Broad in December 2012) during the interference proceeding.

We expect the CVC Group will continue to prosecute patent claims covering inventions included in the Patent Portfolio, which could also result in additional 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. The CVC Group, 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 or 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, EP 3,241,902 B1 and EP 3,401,400. 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 Therapeutics, Caribou, ERS Genomics Ltd., or ERS, and our wholly-owned subsidiary TRACR Hematology Ltd., or 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, 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 U.S. trademark estate consists of 8 pending applications, including for CTX001, CTX101, CTX110, CTX120, CTX130, and CRISPR TX, as well as several U.S. registrations, including for CRISPR THERAPEUTICS and the CRISPR THERAPEUTICS logo. Our international trademark estate consists of 15 pending applications and 3 International Registrations, including a pending application for 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. 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. Charpentier***

In April 2014, we entered into a license agreement, or the Charpentier License Agreement, with Dr. 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 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 sublicense 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 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 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. Charpentier***

In April 2014, concurrently with our license agreement with Dr. Charpentier, TRACR 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 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 2024. TRACR is solely responsible for all clinical, regulatory and development costs.

Under the TRACR License Agreement, Dr. 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. 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.

### *Enabling Technologies*

In support of our lead *ex vivo* programs, we have entered into a commercial license agreement with MaxCyte Incorporated, or 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.

In support of our allogeneic CAR-T platform, we have entered into a license agreement with KSQ Therapeutics Incorporated, or KSQ, whereby we gained access to KSQ intellectual property for editing certain novel gene targets in our allogeneic oncology cell therapy programs, and KSQ gained access to our intellectual property for editing novel gene targets identified by KSQ as part of its current and future engineered tumor infiltrating lymphocyte cell programs.

We have also formed several collaborations to support our *in vivo* programs. We have a collaboration with CureVac AG, or 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, Inc., or 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, or 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 of CRISPR Therapeutics.

### **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 editing, gene therapy and cell therapy 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, substantial competition from many different sources, including large pharmaceutical, specialty pharmaceutical and biotechnology companies; academic institutions and governmental agencies; and public and private research institutions, some or all of which may have greater access to capital or resources than we do. 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 gene-editing technology. We are aware of several companies focused on developing therapies in various indications using CRISPR/Cas9 gene-editing technology, including Intellia Therapeutics and Editas Medicine. In addition, several academic groups have developed new gene-editing technologies based on CRISPR/Cas9, such as base editing and prime editing, that may have utility in therapeutic development. Companies seeking to develop therapies based on these technologies include Beam Therapeutics and Prime Medicine.

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

We are also aware of companies developing therapies in various areas related to our specific research and development programs. In hemoglobinopathies, these companies include Acceleron Pharma, Aruvant Therapeutics, bluebird bio, Editas Medicine, Global Blood Therapeutics, Novartis Pharmaceuticals, Orchard Therapeutics, and Sangamo Therapeutics. In immuno-oncology, these companies include Allogene Therapeutics, bluebird bio, Bristol Myers Squibb, Cellectis, Fate Therapeutics, Gilead Sciences, Novartis Pharmaceuticals, Poseida Therapeutics and Precision BioSciences. In regenerative medicine, these companies include BlueRock Therapeutics (acquired by Bayer in 2019), Sana Biotechnology and Semma Therapeutics (acquired by Vertex in 2019). In *in vivo*, these companies include Editas Medicine, Intellia Therapeutics, Sarepta Therapeutics, Ultragenyx and Verve Therapeutics.

Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition. These new technologies could have advantages over CRISPR/Cas9 gene editing in some applications and 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 CRISPR-associated nuclease, Cas12a (Cpf1), which can also edit human DNA, as well as advanced forms of Cas9. Editas and certain of its scientific founders have asserted that Cas12a may work better than Cas9 in some cases. Cas9 may be determined to be less attractive than Cas12a or other CRISPR proteins that have yet to be discovered. Multiple academic labs and companies have also published on other CRISPR-associated nuclease variants that can edit human DNA.

In addition to competition from other gene-editing therapies or gene or cell 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.

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, 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. 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. 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, see our discussion of the ‘048 interference, the ‘115 interference and European opposition proceedings above in “Business—Intellectual Property—*In-Licensed Intellectual Property from Dr. Charpentier*” and in “Legal Proceedings.”

Furthermore, we may be involved in other interference proceedings or other disputes in the future. 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, or Vilnius, 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, or Harvard, 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.

The 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 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. For example, we and eight other entities opposed the Broad’s EP 2,771,468, or the ‘468 patent. The ‘468 patent was revoked in January 2018; the decision was appealed by the patentees and the appeal will be heard in January 2020. In addition to the ‘468 patent, three other of the Broad’s European patents have been revoked (EP 2,764,103, 2,784,162 and 2,931,898); and two have been maintained but in amended form with substantial limitations in the scope of claims. 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 EU, 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 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 not 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 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 of receipt by the sponsor or its agents after determining that the information qualifies for such expedited 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 or by specifically altering host (human) genetic sequences. Examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid), genetically modified microorganisms (e.g. viruses, bacteria, fungi), engineered site specific nucleases used for human genome editing and ex vivo genetically modified human cells. 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. Depending on the product type, long term follow up can be up to 15 years or as little as five years.

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. In April 2019, NIH announced the updated guidelines, which reflect these proposed changes, and clarified that these trials will remain subject to the FDA's oversight and other clinical trial regulations, and oversight at the local level will continue as set forth in the NIH Guidelines. Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. Only after FDA, IBC and other relevant approvals are in place can these protocols proceed.

### *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, Priority Review and Regenerative Advanced Therapy 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, priority review, and regenerative advanced therapy 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.

Finally, the FDA can accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

### *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 EU***

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 EU generally follows the same lines as in the United States, although the approval of a medicinal product in the United States is no guarantee of approval of the same product in the EU, either at all or within the same timescale as approval may be granted in the United States. The process 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 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 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 EU 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 in relation to the clinical trial. The clinical trial application must be accompanied by an investigational medicinal product dossier with supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and corresponding national laws of the relevant EU 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. 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 EU member states (meaning that no national implementing legislation in each EU member state is required), 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. It is expected that the new Clinical Trials Regulation (EU) No 536/2014 will come into effect following confirmation of full functionality of the Clinical Trials Information System, the centralized EU portal and database for clinical trials foreseen by the new Clinical Trials Regulation, through an independent audit.

## *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 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 (as well as Iceland, Norway and Liechtenstein). 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 those products for which the use of the centralized procedure is not mandatory, applicants may elect to use the centralized procedure where either the product contains a new active substance indicated for the treatment of other diseases, or where the applicant can show that the product constitutes a significant therapeutic, scientific or technical innovation or for which a centralized process is in the interest of patients at an EU level.

Specifically, the grant of marketing authorization in the EU for products containing viable human tissues or cells such as gene therapy medicinal products is governed by Regulation (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 the Committee for Advanced Therapies, or CAT, at EMA, which provides an opinion regarding the application for marketing authorization for an advanced therapy medicinal product. 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 whether a product meets the required quality, safety and efficacy requirements, and whether a product has a positive benefit/risk profile. Under the centralized procedure in the EU, the maximum timeframe for the evaluation of an MAA is 210 days from receipt of a valid MAA, 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. Clock stops may extend the timeframe of evaluation of an MAA considerably beyond 210 days. Where the CHMP gives a positive opinion, it provides the opinion, together with supporting documentation, to the European Commission, who make the final decision to grant a marketing authorization. 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 frame of 210 days for assessment will be reduced to 150 days (excluding clock stops), but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that the application is no longer appropriate to conduct an accelerated assessment.

### *PRIME scheme*

EMA now offers a scheme that is intended to reinforce early dialogue with, and regulatory support from, EMA in order to stimulate innovation, optimize development and enable accelerated assessment of PRiority Medicines, or PRIME. It is intended to build upon the scientific advice scheme and accelerated assessment procedure offered by EMA. The scheme is voluntary and eligibility criteria must be met for a medicine to qualify for PRIME.

The PRIME scheme is open to medicines under development and for which the applicant intends to apply for an initial marketing authorization application through the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (meaning there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods or therapy or improving existing ones. Applicants will typically be at the exploratory clinical trial phase of development, and will have preliminary clinical evidence in patients to demonstrate the promising activity of the medicine and its potential to address, to a significant extent, an unmet medical need. In exceptional cases, applicants from the academic sector or SMEs (small and medium sized enterprises) may submit an eligibility request at an earlier stage of development if compelling non-clinical data in a relevant model provide early evidence of promising activity, and first in man studies indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability.



If a medicine is selected for the PRIME scheme, the EMA:

- appoints a rapporteur from the CHMP or from the CAT to provide continuous support and to build up knowledge of the medicine in advance of the filing of a marketing authorization application;
- issues guidance on the applicant's overall development plan and regulatory strategy;
- organises a kick-off meeting with the rapporteur and experts from relevant EMA committees and working groups;
- provides a dedicated EMA contact person; and
- provides scientific advice at key development milestones, involving additional stakeholders, such as health technology assessment bodies and patients, as needed.

Medicines that are selected for the PRIME scheme are also expected to benefit from EMA's accelerated assessment procedure at the time of application for marketing authorization. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

### *Regulatory Data Protection in the EU*

In the EU, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon grant of a marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. 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 period. 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, are strictly regulated in the EU under Directive 2001/83/EC, as amended. The advertising of prescription-only medicines to the general public is not permitted in the EU.

### *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 (i) and (ii), 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. The grant of a 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 the same therapeutic indication in respect of 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. There are a number of derogations from the ten-year period of market exclusivity pursuant to which the European Commission may grant a marketing authorization for a similar medicinal product in the same therapeutic indication, including where the second applicant can establish that although their product is similar to the orphan medicinal product already authorized, the second product is safer, more effective or otherwise clinically superior.

For other markets in which we might in the 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 EU, 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 EU 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. EU member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other EU 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 EU have increased the level of discounting required in relation to the pricing of pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic, and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

### ***Healthcare Law and Regulation***

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of pharmaceutical products that are granted marketing approval. Arrangements with providers, consultants, third-party payors, and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to 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, in exchange for or intended 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 (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) 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, effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- federal 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 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 70% 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, increased pursuant to the Bipartisan Budget Act of 2018 which became effective as of 2019;
- 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 2029 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, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. Various portions of the ACA are currently undergoing legal and constitutional challenges in the Fifth Circuit Court and the United States Supreme Court; the Trump Administration has issued various Executive Orders which eliminated cost sharing subsidies and various provisions 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; and Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended. We cannot predict what affect further changes to the ACA would have on our business.

Further, CMS recently finalized regulations that 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. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. It is unclear what type of impact, if any, efforts such as this 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 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a 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, 2019, we had 304 full-time employees, 104 of whom held Ph.D. or M.D. degrees, 252 of whom were engaged in research and development, and 52 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. We generated net income of \$66.9 million for the year ended December 31, 2019, but our net loss was \$165.0 million and \$68.4 million for the years ended December 31, 2018 and 2017, respectively. As of December 31, 2019 and 2018, we had an accumulated deficit of \$224.7 million and \$291.6 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 various programs;
- 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 IND supporting preclinical studies and initiate clinical trials for our product candidates;
- 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;
- establish or contract for manufacturing capabilities if we obtain regulatory approvals to manufacture our product candidates;
- 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. For example, while we were profitable for the year ended December 31, 2019 due to collaboration revenue from Vertex and our gain resulting from the consolidation of Casebia, we do not expect to sustain our profitability in future years.

*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, 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, 2019, and 2018, we had cash of approximately \$943.8 million and \$456.6 million, respectively. In November 2019, we completed an offering of an aggregate of 4.9 million common shares, which were sold at a price to the public of \$64.50 per share for aggregate net proceeds of \$294.4 million, which were net of equity issuance costs of \$20.7 million. With our cash on hand as of December 31, 2019, we expect cash and cash equivalents to be sufficient to fund our 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 collaborations with Vertex and ViaCyte;
- 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 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 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. Tax losses are only finally assessed by the tax authorities when offset with taxable profit (which will not be the case if 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.

The effective corporate income tax rate in the Canton of Zug for 2019 amounts to 14.35% (federal, cantonal and communal). As already mentioned above, no tax ruling was filed with the Zug tax authorities for applying for the taxation as mixed company. However, up until and including the tax period 2019 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, assuming we fulfill the respective criteria. The effective corporate income tax rate as mixed company in the Canton of Zug ranges between 8.53% and 9.55% on the profit before taxes, 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.

As of January 1, 2020, the Canton of Zug introduced its law on the corporate tax reform. According to this new law, the ordinary effective corporate income tax rate has been reduced to 11.91% (federal, cantonal and communal) and, among others, the privileges for mixed companies have been abolished. Furthermore, a number of additional tax benefits are implemented, including but not limited to generous rules for companies, which were previously taxed as mixed companies (e.g. special tax rate or step up of the tax based followed by tax effective depreciations in the following years). Determining which of these options would be most favorable and to what extent these rules are beneficial for us, depends on the development of our taxable profit during this period and must be assessed in the upcoming year.

### ***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. 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 collaboration agreements with Vertex and ViaCyte and option agreement with Bayer, 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.

We must file U.S. investigational new drug applications, or INDs, clinical trial applications, or CTAs, or their equivalents with regulatory authorities to commence clinical trials. 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. In addition, commencing any of our clinical trials is also subject to acceptance by the European regulatory authorities, or its equivalent, 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, FDA or their equivalent 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 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 EU;
- 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 EU.*

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 EU and only a limited number of clinical trials of product candidates 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. For example, because we have only very limited data from clinical trials in CTX001, we have not yet been able to fully assess safety in humans. In addition, because we have only recently commenced clinical trials for certain of our other product candidates, we have not yet been able to assess safety in humans. 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 EU 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.

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. In January 2020, the FDA issued several new guidance documents on gene therapy products. 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 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 EU 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 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 with 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 of eligible prospective patients that are otherwise eligible patients for competitive clinical trials;
- 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 our value 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 EU 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, as a company, 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.

*Breakthrough Therapy Designation, Fast Track Designation, Regenerative Medicine Advanced Therapy Designation or Priority Review by the FDA, Orphan Drug Designation by the European Commission or PRIME Scheme by the EMA, Even If Granted for Any of Our Product Candidates, May Not Lead to a Faster Development, Regulatory Review or Approval Process, and It May Not Increase the Likelihood That Any of Our Product Candidates Will Receive Marketing Approval.*

We may seek a Breakthrough Therapy Designation for some of our product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA may also be eligible for priority review and accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

We may seek Fast Track Designation for some of our product candidates. For instance, CTX001 has been granted Fast Track Designation by the FDA for the treatment of TDT and SCD. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation; we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Fast Track Designation alone does not guarantee qualification for the FDA's priority review procedures.

We may seek Regenerative Medicine Advanced Therapy, or RMAT, designation for one or more of our product candidates. In 2017, the FDA established the RMAT designation as part of its implementation of the 21st Century Cures Act to expedite review of any drug that meets the following criteria: it qualifies as a RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition. Like Breakthrough Therapy Designation, RMAT designation provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate, and eligibility for rolling review and priority review. Products granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites. RMAT-designated products that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of the therapy. There is no assurance that we will be able to obtain RMAT designation for any of our product candidates. RMAT designation does not change the FDA's standards for product approval, and there is no assurance that such designation will result in expedited review or approval or that the approved indication will not be narrower than the indication covered by the designation. Additionally, RMAT designation can be revoked if the criteria for eligibility cease to be met as clinical data emerges.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily result in expedited regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

We may seek orphan drug designation, or ODD, from the European Commission for one or more of our product candidates. For instance, CTX001 has been granted ODD by the European Commission for the treatment of TDT and SCD. An ODD provides a number of benefits, including fee reductions, regulatory assistance, and the ability to apply for a centralized EU marketing authorization. The grant of a 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 the same therapeutic indication in respect of a "similar medicinal product." However, the market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for ODD because, for example, the product is sufficiently profitable not to justify market exclusivity. There are a number of derogations from the ten-year period of market exclusivity pursuant to which the European Commission may grant a marketing authorization for a similar medicinal product in the same therapeutic indication, including where the second applicant can establish that although their product is similar to the orphan medicinal product already authorized, the second product is safer, more effective or otherwise clinically superior. There is no assurance that we will be able to obtain ODD for any of our other product candidates. ODD does not change the standards for product approval, and there is no assurance that such designation will result in expedited review or approval.

Finally, we may seek to qualify our product candidates under the PRiOritY MEDicines, or PRIME, scheme from the EMA. The PRIME scheme is open to medicines under development and for which the applicant intends to apply for an initial marketing authorization application through the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods or therapy or improving existing ones. There is no assurance that we will be able to obtain PRIME qualification for any of our product candidates. PRIME does not change the standards for product approval, and there is no assurance that such qualification will result in expedited review or approval. Moreover, where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

*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, a group of 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. Additionally, in November 2018, Dr. Jiankui He, a biophysics researcher who was an associate professor in the Department of Biology of the Southern University of Science and Technology in Shenzhen, China, reportedly claimed he had created the first human genetically edited babies, twin girls. This claim, and another that Dr. He had helped create a second gene-edited pregnancy, was subsequently confirmed by Chinese authorities and was negatively received by the public, in particular by those in the scientific community. News reports indicate that Dr. He was sentenced to three years in prison and fined \$430,000 in December 2019 by the Chinese government for illegal medical practice in connection with such activities. In the wake of the claim, the World Health Organization established a new advisory committee to create global governance and oversight standards for human gene editing. 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 and has also released principles for the use of gene editing in therapeutic applications endorsed by a number of companies that use gene-editing technologies. 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, Or Any Collaborators We May Have, Obtain Marketing Approval Could Be Subject To Restrictions Or Withdrawal From The Market, And We Or They May Be Subject To Substantial Penalties If We Or They Fail To Comply With Regulatory Requirements Or If We Or They 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, or any collaborators we may have, do not market our products for their approved indications, we or they 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 or other collaborators' 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 or our collaborators 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 or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, we or our collaborators may lose any marketing approval that we or our collaborators 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, including investigations of any of our vendors, 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 or our collaborators' 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 EU 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, the EMA or other regulatory authorities;
- 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 editing, gene therapy and cell therapy 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, substantial competition from many different sources, including large pharmaceutical, specialty pharmaceutical and biotechnology companies; academic institutions and governmental agencies; and public and private research institutions, some or all of which may have greater access to capital or resources than we do. 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 gene-editing technology. We are aware of several companies focused on developing therapies in various indications using CRISPR/Cas9 gene-editing technology, including Intellia Therapeutics and Editas Medicine. In addition, several academic groups have developed new gene-editing technologies based on CRISPR/Cas9, such as base editing and prime editing, that may have utility in therapeutic development. Companies seeking to develop therapies based on these technologies include Beam Therapeutics and Prime Medicine

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

We are also aware of companies developing therapies in various areas related to our specific research and development programs. In hemoglobinopathies, these companies include Acceleron Pharma, Aruvant Therapeutics, bluebird bio, Editas Medicine, Global Blood Therapeutics, Novartis Pharmaceuticals, Orchard Therapeutics and Sangamo Therapeutics. In immuno-oncology, these companies include Allogene Therapeutics, bluebird bio, Bristol Myers Squibb, Cellectis, Fate Therapeutics, Gilead Sciences, Novartis Pharmaceuticals, Poseida Therapeutics and Precision BioSciences. In regenerative medicine, these companies include BlueRock Therapeutics (acquired by Bayer in 2019), Sana Biotechnology and Semma Therapeutics (acquired by Vertex in 2019). In *in vivo*, these companies include Editas Medicine, Intellia Therapeutics, Sarepta Therapeutics, Ultragenyx and Verve Therapeutics.

Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition. These new technologies could have advantages over CRISPR/Cas9 gene editing in some applications and 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 CRISPR-associated nuclease, Cas12a (Cpf1), which can also edit human DNA, as well as advanced forms of Cas9. Editas and certain of its scientific founders have asserted that Cas12a may work better than Cas9 in some cases. Cas9 may be determined to be less attractive than Cas12a or other CRISPR proteins that have yet to be discovered. Multiple academic labs and companies have also published on other CRISPR-associated nuclease variants that can edit human DNA.

In addition to competition from other gene-editing therapies or gene or cell 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.

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, 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. 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. 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.

Moreover, 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 our value and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in our value 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. Third-party payors, such as private health insurers, health maintenance organizations, and governmental programs such as Medicare and Medicaid, 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. Governmental and private 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. For example, in October 2015, we entered into the 2015 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 June 2019, we entered into the 2019 Collaboration Agreement with Vertex to develop and commercialize products for the treatment DMD and DM1.

Under our 2015 Collaboration Agreement with Vertex, Vertex had sole authority to select genetic targets to pursue and we do 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. Additionally, under the 2019 Collaboration Agreement with Vertex, Vertex has sole authority to develop and commercialize products under the agreement (subject to our option to co-develop and co-commercialize products for the treatment of DM1). Our lack of control over the clinical development and commercialization activities in our agreements with 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 in a timely fashion, if at all, or the completion or delay in BLA filings.

In addition, the termination of our agreements with Vertex would prevent us from receiving any milestone, royalty payments and other benefits under that agreement, which may 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 agreements, we will be restricted from granting rights to other parties to use our gene-editing technology to pursue therapies that address these genetic targets. The non-competition provisions in this agreement 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 on 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 the 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 and require significantly greater expenditures.

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. In addition, if our contract manufacturers are unable to timely perform or become distracted as a result of actions taken by the FDA or a comparable health regulatory authority, we may experience manufacturing delays or may need to find alternative manufacturing facilities, which in each case, 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 products 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, in exchange for or intended 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. 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 or fraudulent claim for purposes of the False Claims Act;
- HIPAA, as further amended by 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 (currently defined to include doctors, dentists, optometrists, podiatrists and chiropractors) 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; effective January 1, 2022, these reporting obligations will extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners; 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.

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

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

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. 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, 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.

*Swiss Corporate Governance With Respect To Executive Compensation May Affect Our Business.*

The Swiss Federal Council Ordinance Against Excessive Compensation at Public Companies, or the Ordinance, among other things, (a) requires a binding shareholder "say on pay" vote with respect to the compensation of members of our executive management and board of directors, (b) generally prohibits the making of severance, advance, transaction premiums and similar payments to members of our executive management and board of directors and (c) requires companies to specify various compensation-related matters in their articles of association, thus requiring them to be approved by a shareholders' vote. At our annual general meetings, our shareholders are required to approve the maximum aggregate compensation of our board of directors and our executive management team. The Ordinance further provides for criminal penalties against directors and members of executive management in case of non-compliance with certain of its requirements. The Ordinance may negatively affect our ability to attract and retain executive management and members of our board of directors.

*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, 2019, we had 304 full-time employees and we expect to continue to increase our number of employees and the scope of our operations in 2020 and beyond as we 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, commercial partners, and principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the EU and other jurisdictions, provide accurate information to the FDA, the 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.

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 have obtained product liability insurance coverage, 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, or EEA. As a result, we are subject to additional privacy laws. The General Data Protection Regulation, (EU) 2016/679, or 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 have implemented national laws which may partially deviate from the GDPR and impose different and more restrictive 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 member state nations to enact laws that 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 EU, subsequent invocation of Article 50 of the Lisbon Treaty on March 29, 2017, and the United Kingdom is formally leaving the EU on January 31, 2020.

*Legal, political and economic uncertainty surrounding the exit of the U.K. from the 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, commonly referred to as Brexit. Pursuant to Article 50 of the Treaty on EU, the U.K. ceased being a Member State of the EU on January 31, 2020. However, the terms of the withdrawal have yet to be fully negotiated. The implementation period began February 1, 2020 and will continue until December 31, 2020. During this 11-month period, the U.K. will continue to follow all of the EU's rules, the EU's pharmaceutical law remains applicable to the U.K., and the U.K.'s trading relationship will remain the same. However, 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 medicine licensing and regulations, immigration laws and employment laws), have yet to be addressed. This lack of clarity on future U.K. laws and regulations and their interaction with the EU laws and regulations 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 agreements 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. Since the regulatory framework in the U.K. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime with respect to the approval of our product candidates in the U.K. For instance, in November 2017, EU member states voted to move the EMA, the EU's regulatory body, from London to Amsterdam. Operations in Amsterdam commenced in March 2019, and the move itself may cause significant disruption to the regulatory approval process in Europe. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the U.K. Any delay in obtaining, or an inability to obtain, any regulatory approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the U.K. and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the U.K. and/or EU for our product candidates, which could significantly and materially harm our business. 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 United States 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.

We continue to expand our operations, and our corporate structure and tax structure is 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 us and other entities such as partners and licensees, and between us and our subsidiaries. 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. Emmanuelle Charpentier, we exclusively license 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 Patent Portfolio to-date includes, for example, more than fifty (50) granted or allowed patents in the United States, United Kingdom, Germany, Europe, Japan, China, Ukraine, New Zealand, Singapore, Australia, Mexico, Tunisia, Hong Kong, Israel, Peru, the Philippines, 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 pre-issuance 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 an IND (or its equivalent in a major market country) by April 2021 and an obligation to file an IND (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 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 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 USPTO between the claims from one Patent Portfolio patent application (now issued as U.S. Patent No. 10,266,850) 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. The interference was redeclared in March 2016 to add a U.S. patent application owned by the Broad. 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 CVC Group patent application’s claims were broader in scope in that they were not restricted to use in eukaryotic cells, whereas the 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, the CVC Group 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. However, in June 2019, we received notification that the USPTO initiated another interference proceeding between fourteen (14) pending U.S. patent applications co-owned by the CVC Group and thirteen (13) patents and a patent application owned by the Broad. The Broad patents include those that were the subject of the earlier, now-terminated interference. 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, ToolGen, Sigma-Aldrich (a subsidiary of Merck KGaA) and Harvard, have filed patent applications claiming CRISPR/Cas9-related inventions around or within a year after the first CVC Group 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 the CVC Group. In fact, in July 2019 and again in October 2019, Sigma-Aldrich filed petitions with USPTO and the PTAB seeking an interference between itself and the CVC Group that would parallel the ‘115 interference; in September 2019, Toolgen filed a similar petition also seeking an interference between itself and the CVC Group that would parallel the ‘115 interference. The PTAB dismissed Sigma-Aldrich’s first petition in September 2019, but has yet to decide its second petition or the petition filed by Toolgen. Thus, the USPTO may, in the future, declare an interference between certain CVC Group patent applications and one or more Toolgen or Sigma-Aldrich patent applications. The CVC Group 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 the CVC Group, 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, the CVC Group or the other third parties could seek judicial review of their inventorship claims. If the CVC Group 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, the 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 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 the 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 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 Therapeutics. 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 On Compliance with Various Procedural, Document Submission, Fee Payment and Other Requirements Imposed by Governmental Patent Agencies, And Our Patent Protection Could be Reduced or Eliminated For Non-Compliance With These Requirements.*

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

*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 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 \$74.00 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, 2019. 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 27.3% of our common shares, based on the number of common shares outstanding as of February 7, 2020. 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, or *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.

*As A Swiss Corporation, We Are Subject To Swiss Legal Provisions That May Limit Our Flexibility To Swiftly Implement Certain Initiatives Or Strategies.*

We are required, from time to time, to evaluate the carrying amount of our investments in affiliates, as presented on our Swiss standalone balance sheet. If we determine that the carrying amount of any such investment exceeds its fair value, we may conclude that such investment is impaired. The recognized loss associated with such a non-cash impairment could result in our net assets no longer covering our statutory share capital and statutory capital reserves. Under Swiss law, if our net assets cover less than 50 percent of our statutory share capital and statutory capital reserves, the board of directors must convene a general meeting of shareholders and propose measures to remedy such a capital loss. The appropriate measures depend on the relevant circumstances and the magnitude of the recognized loss and may include seeking shareholder approval for offsetting the aggregate loss, or a portion thereof, with our statutory capital reserves including qualifying additional paid-in capital otherwise available for distributions to shareholders or raising new equity. Depending on the circumstances, we may also need to use qualifying additional paid-in capital available for distributions in order to reduce our accumulated net loss and such use might reduce our ability to make distributions without subjecting our shareholders to Swiss withholding tax. These Swiss law requirements could limit our flexibility to swiftly implement certain initiatives or strategies.

*Anti-takeover Provisions In Our Articles Of Association Could Make An Acquisition Of Our Company, Which May Be Beneficial To Our Shareholders, More Difficult And May Prevent Attempts By Our Shareholders To Replace Or Remove Our Current Management.*

Provisions in our articles of association may discourage, delay or prevent an acquisition of our Company or changes in the composition of our board of directors. Among other things, these provisions require the approval of at least two thirds of represented shares present or voting at a shareholder meeting for the removal of a member of our board of directors and to increase the maximum number of members of our board of directors; limit the accumulated voting rights of any person or entity to 15% of our registered share capital; limit the voting rights of an acquirer of more than 5% of our registered share capital in a transaction or series of transactions in which our board of directors did not provide for an exemption, which could prevent or delay a change in control of our Company; provide that the board of directors is authorized, subject to obtaining shareholder approval every two years, at any time during a maximum two-year period, which under our current authorized share capital will expire on June 10, 2021, to issue a specified number of shares, which under our current authorized share capital is approximately thirty-two percent of the share capital registered in the commercial register, and to limit or withdraw the preemptive rights of existing shareholders in various circumstances; provide for a conditional share capital that authorizes the issuance of additional shares up to a maximum amount of approximately thirty-nine percent of the share capital registered in the commercial register, without obtaining additional shareholder approval, (i) through the exercise of conversion and/or option rights granted in connection with bonds or similar instruments, including convertible debt instruments, and (ii) in connection with the exercise of options granted to employees or other service providers of the Company or any of its subsidiaries; and provide that a merger or demerger transaction requires the affirmative vote of at least two thirds of the shares represented at a shareholders' meeting.

Although we believe these provisions collectively provide for an opportunity to obtain greater value for shareholders by requiring potential acquirors to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some shareholders. In addition, these provisions may frustrate or prevent any attempts by our shareholders to replace or remove our current management by making it more difficult for shareholders to replace members of our board of directors, which is responsible for appointing the members of our management.

*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. The authorized share capital approved by our shareholders will expire on June 10, 2021 and is limited to approximately thirty-two percent of our registered share capital pursuant to the articles of association in force. 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 standalone 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.

Dividends and similar cash or in-kind distributions made by the Company to a shareholder (including liquidation proceeds and stock dividends) are subject to Swiss withholding tax (*Verrechnungssteuer*), currently at a rate of 35% (applicable to the gross amount of the taxable distribution). The Company is obliged to deduct the Swiss withholding tax from the gross amount of any taxable distribution and to pay the tax to the Swiss Federal Tax Administration within 30 calendar days of the due date of such distribution. However, the repayment of the nominal value of the shares and any repayment of qualifying additional paid-in capital (capital contribution reserves (*Reserven aus Kapitaleinlagen*)) are not subject to Swiss withholding tax. The Swiss withholding tax will also apply to payments (exceeding the respective share capital and used capital contribution reserves) upon a repurchase of shares by the Company, (i) if the Company’s share capital is reduced upon such repurchase (redemption of shares), (ii) if the total of repurchased shares exceeds 10% of the Company’s share capital or (iii) if the repurchased shares are not resold within six years after the repurchase. This six-year deadline to resell the repurchased shares is suspended for so long as the shares are reserved to cover obligations under convertible bonds, option bonds or employee stock option plans (in the case of employee stock option plans, the maximum suspension is six years). In the event of a taxable share repurchase, Swiss withholding tax is imposed on the difference between the repurchase price and the sum of the nominal value of the repurchased shares and capita contribution reserves paid back upon the repurchase.

Swiss resident individuals who hold their shares as private assets, or Resident Private Shareholders, are in principle eligible for a full refund or credit against income tax of the Swiss withholding tax if they duly report the underlying income in their income tax return. In addition, (i) corporate and individual shareholders who are resident in Switzerland for tax purposes, (ii) corporate and individual shareholders who are not resident in Switzerland, and who, in each case, hold their shares as part of a trade or business carried on in Switzerland through a permanent establishment with fixed place of business situated in Switzerland for tax purposes and (iii) Swiss resident private individuals who, for income tax purposes, are classified as “professional securities dealers” for reasons of, inter alia, frequent dealing, or leveraged investments, in shares and other securities (collectively, “Domestic Commercial Shareholders”) are in principle eligible for a full refund or credit against income tax of the Swiss withholding tax if they duly report the underlying income in their income statements or income tax return, as the case may be.

Shareholders who are not resident in Switzerland for tax purposes, and who, during the respective taxation year, have not engaged in a trade or business carried on through a permanent establishment with fixed place of business situated in Switzerland for tax purposes, and who are not subject to corporate or individual income taxation in Switzerland for any other reason (collectively, “Non-Resident Shareholders”) may be entitled to a total or partial refund of the Swiss withholding tax if the country in which such recipient resides for tax purposes maintains a bilateral treaty, or Tax Treaty, for the avoidance of double taxation with Switzerland and further conditions of such Tax Treaty are met.

A U.S. shareholder that qualifies for benefits under the U.S.-Swiss Tax 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% voting rights, or for a full refund in the case of qualified pension funds). Non-Resident Shareholders should be aware that the procedures for claiming treaty benefits (and the time required for obtaining a refund) may differ from country to country. Non-Resident Shareholders should consult their own legal, financial or tax advisors regarding receipt, ownership, purchases, sale or other dispositions of shares and the procedures for claiming a refund of the Swiss withholding tax.



*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, or the Code, who owns or is considered to own 10% or more of (1) the total combined voting power of all classes of stock entitled to vote or (2) the value of all classes of stock of such corporation. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain.

During our 2019 taxable year we believe that we did not have shareholders that were Ten Percent Shareholders for United States federal income tax purposes. However, our CFC status for the taxable year ended December 31, 2019 and our current taxable year is unknown and we may be a CFC for the taxable year ended December 31, 2019, 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). However, IRS guidance on which taxpayers such as us can rely may permit us to avoid certain negative consequences of these changes, and we expect to consider the availability and advisability of relying on this guidance. 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 passive foreign investment company, or 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 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 2018 taxable year, we provided information necessary for our shareholders to make a qualified electing fund, or QEF, election with respect to us for the 2018 taxable year. We provided such information on our website ([www.crisprtx.com](http://www.crisprtx.com)). A U.S. holder that makes a QEF election with respect to our shares is required to include a pro rata share of our income on a current basis, whether or not we make distributions. For the 2018 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 2019 taxable year, it is possible that we may be a PFIC for the 2019 taxable year as well. We were in a net income position for the 2019 taxable year. While we have not yet determined what our ordinary earnings and net capital gain was in 2019 for purposes of the QEF inclusion rules, the consequences of our treatment as a PFIC may be more adverse to U.S. holders than in prior years as a result. We will endeavor to provide to you, for each taxable year that 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. Alternatively, a U.S. holder may be able to make a mark-to-market election, assuming that our shares constitute “marketable” securities under the Code, which generally avoids the adverse consequences of PFIC status discussed above, but would require a U.S. holder to annually report as ordinary income any increase in value of our shares during the year (as well as generally allowing deductions for any decrease in the value of our shares).

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 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. 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 or a mark to market election with respect to us, and the application of the PFIC rules to any of our subsidiaries. See “Risk Factor—*Comprehensive Tax Reform Legislation Could Adversely Affect Our Business And Financial Condition.*”

*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. Our U.S. headquarters are located at 610 Main Street, Cambridge, Massachusetts where we lease approximately 98,064 square feet of laboratory and office space under two separate subleases that expire in March 2024 and December 2026, respectively. We have an option to extend the term of each of these subleases for five years if, at the time of expiration of the initial term, the sublessor does not intend to utilize the space for itself or its affiliates. A portion of this space is subject to a sub-sublease with a third party. We also have business offices elsewhere in Cambridge, Massachusetts, San Francisco, California and London, United Kingdom. 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 USPTO declared an interference (Interference No. 106,048, or '048 interference) between one of the then pending U.S. patent applications (now issued as US Patent No. 10,266,850) 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 the Broad. The interference was redeclared in March 2016 to add a U.S. patent application owned by the Broad. An interference is a proceeding conducted at the USPTO by the 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, California, and Vienna, which we refer to collectively as the "CVC Group", and the Broad.

Following motions by the parties and other procedural matters, in February 2017, the PTAB concluded that the '048 interference should be dismissed. In its decision, the PTAB concluded that, although the claims overlap, the respective scope of the CVC Group's and the Broad's claim sets as presented did not define the same patentable invention and, accordingly, terminated the '048 interference.

In April 2017, the CVC Group appealed the PTAB's decision to the Federal Circuit. In the appeal, the CVC Group asked the court to review and reverse the PTAB's February 2017 decision, which terminated the '048 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 '048 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 issued as U.S. Patent No. 10,266,850.

In June 2019, we received notification that the USPTO initiated a new interference proceeding at the PTAB, which the PTAB redeclared in August 2019. The '115 interference involves fourteen (14) pending U.S. patent applications co-owned by the CVC Group and thirteen (13) patents and a patent application owned by the Broad. Specifically, the PTAB declared the '115 interference between the CVC Group's pending U.S. Patent Application Nos. 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; 16/136,175; 16/276,361; 16/276,365; 16/276,368; and 16/276,374, and the Broad's U.S. Patent Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; 9,840,713, and U.S. Patent Application No. 14/704,551. This list includes the same twelve Broad patents and application that were involved in the '048 interference. In contrast, none of the issued U.S. patents the CVC Group owns are subject to this proceeding. The CVC Group's inventions that are the subject of the '115 interference were first filed with the USPTO in May of 2012, while the Broad filed its first application seven months later in December of 2012. However, the 14 CVC Group patent applications that are involved in the '115 interference are continuing patent applications that were filed in 2018 and claim priority to the CVC Group's original 2012 filing, while the Broad's involved patents and patent application were filed between 2013 and 2015. Because the PTAB accorded neither party the benefit of any of its first filing dates, but instead accorded only the benefit of the actual filing dates of the involved patents and patent applications, the CVC Group was by default named the Junior Party. Both parties have filed motions requesting the benefit of their earliest priority dates (CVC in May of 2012 and the Broad in December of 2012) during 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 an additional 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 and in 2019, several parties filed oppositions in the European Patent Office to the grant of both our second and third 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

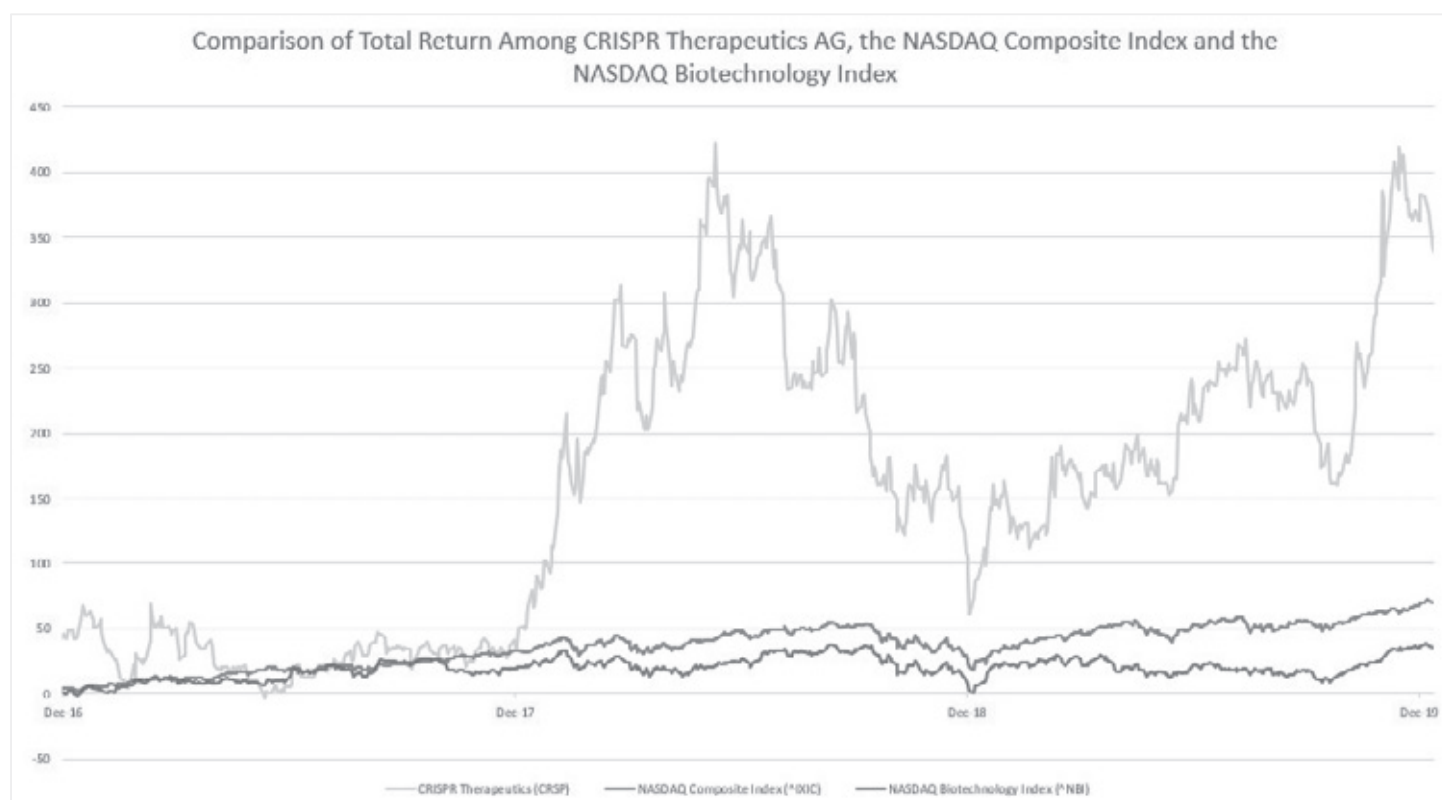
Our common shares are traded on The Nasdaq Global Market under the symbol “CRSP.”

#### 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, 2019, 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 shares, 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 7, 2020, we had approximately 8 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.

**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.

	2019	2018	December 31, 2017	2016	2015
	(in thousands, except share and per share amounts)				
<b>Consolidated Statements of Operations Data:</b>					
Collaboration revenue	\$ 289,590	\$ 3,124	\$ 40,997	\$ 5,164	\$ 247
Operating expenses:					
Research and development	179,362	113,773	69,800	42,238	12,573
General and administrative	63,488	48,294	35,845	31,056	13,403
Total operating expenses	242,850	162,067	105,645	73,294	25,976
Income (loss) from operations	46,740	(158,943)	(64,648)	(68,130)	(25,729)
Other income (expense), net	20,566	(5,485)	(1,960)	45,412	(92)
Net income (loss) before income taxes	67,306	(164,428)	(66,608)	(22,718)	(25,821)
Provision for income taxes	(448)	(553)	(1,749)	(484)	(7)
Net income (loss)	66,858	(164,981)	(68,357)	(23,202)	(25,828)
Foreign currency translation adjustment	15	(22)	40	(18)	(6)
Comprehensive income (loss)	\$ 66,873	(165,003)	(68,317)	\$ (23,220)	\$ (25,834)
Reconciliation of net income (loss) to net income (loss) attributable to common shareholders:					
Net income (loss)	\$ 66,858	\$ (164,981)	\$ (68,357)	\$ (23,220)	\$ (25,828)
Loss attributable to noncontrolling interest	—	—	—	25	325
Net income (loss) attributable to common shareholders	\$ 66,858	\$ (164,981)	\$ (68,357)	\$ (23,177)	\$ (25,503)
Net income (loss) per share attributable to common shareholders—basic	\$ 1.23	\$ (3.44)	\$ (1.71)	\$ (1.89)	\$ (5.06)
Weighted-average common shares outstanding used in net income (loss) per share attributable to common shareholders—basic	54,392,304	47,964,368	40,057,365	12,257,483	5,037,404
Net income (loss) per share attributable to common shareholders—diluted	\$ 1.17	\$ (3.44)	\$ (1.71)	\$ (1.89)	\$ (5.06)
Weighted-average common shares outstanding used in net income (loss) per share attributable to common shareholders—diluted	56,932,798	47,964,368	40,057,365	12,257,483	5,037,404
	2019	2018	December 31, 2017	2016	2015
	(in thousands)				
<b>Consolidated Balance Sheet Data:</b>					
Cash	\$ 943,771	\$ 456,649	\$ 239,758	\$ 315,520	\$ 155,961
Working capital	930,441	438,649	233,874	298,190	146,685
Total assets	1,066,752	489,016	271,346	344,962	159,423
Redeemable convertible preferred shares	—	—	—	—	64,521
Total shareholders' equity (deficit)	939,425	392,195	187,832	232,846	(29,124)

## 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.*

### 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 such diseases. 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.

We have established a portfolio of therapeutic programs across a broad range of disease areas including hemoglobinopathies, oncology, regenerative medicine and rare diseases.

Our lead product candidate, CTX001, is an investigational, autologous, gene-edited hematopoietic stem cell therapy that is being evaluated for the treatment of transfusion-dependent beta thalassemia, or TDT, and severe sickle cell disease, or SCD. CTX001 is being developed under a co-development and co-commercialization agreement between us and Vertex.

We and Vertex are investigating CTX001 in a Phase 1/2 open-label clinical trial, CLIMB THAL-111, that is 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 the initial two patients, the trial will open for broader concurrent enrollment. CLIMB THAL-111 is designed to enroll up to 45 patients and follow patients for approximately two years after infusion. Each patient will be asked to participate in a long-term follow-up study. CTX001 has been granted Fast Track Designation by the FDA for the treatment of TDT, as well as has been granted orphan drug designation, or ODD, by the European Commission. Enrollment is ongoing at multiple clinical trial sites globally. In the fourth quarter of 2019, we released preliminary clinical data from the first patient treated with CTX001 with TDT, and we expanded the TDT patient population for CTX001 to include beta zero/beta zero subtypes.

We and Vertex are also investigating CTX001 in a Phase 1/2 open-label clinical trial, CLIMB SCD-121, that is 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 the initial two patients, the trial will open for broader concurrent enrollment. CLIMB SCD-121 is designed to enroll up to 45 patients and follow patients for approximately two years after infusion. Each patient will be asked to participate in a long-term follow-up study. CTX001 has been granted Fast Track Designation by the FDA for the treatment of SCD, as well as ODD by the European Commission. Enrollment is ongoing at multiple clinical trial sites globally. In the fourth quarter of 2019, we released preliminary clinical data from the first patient treated with CTX001 with severe SCD.

In addition, we are developing our own portfolio of CAR-T cell product candidates based on our gene-editing technology. Our lead candidate, CTX110, is a healthy donor-derived gene-edited allogeneic CAR-T therapy targeting CD19 for the treatment of CD19<sup>+</sup> malignancies. We are investigating CTX110 in a Phase 1/2 clinical trial that is designed to assess the safety and efficacy of CTX110 in relapsed or refractory B-cell malignancies. The multi-center, open-label clinical trial is designed to enroll up to 95 patients and investigate several dose levels of CTX110. The study is currently enrolling at multiple clinical trial sites globally. Our second gene-edited allogeneic CAR-T program, CTX120, targets B-cell maturation antigen. We are investigating CTX120 in a Phase 1 clinical trial that is designed to assess the safety and efficacy of CTX120 in relapsed or refractory multiple myeloma. The multi-center, open-label clinical trial is designed to enroll up to 80 patients and investigate several dose levels of CTX120. The trial is currently enrolling. Our third gene-edited CAR-T candidate, CTX130, targets CD70. CTX130 is in development for the treatment of both solid tumors, such as renal cell carcinoma, and T-cell and B-cell hematologic malignancies.



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. We maintain three broad strategic partnerships to develop gene editing-based therapeutics in specific disease areas.

*Vertex.* We established our initial collaboration agreement in 2015 with Vertex, which focused on TDT, SCD, cystic fibrosis and select additional indications. In December 2017, we entered into a joint development and commercialization agreement with Vertex to co-develop and co-commercialize CTX001 as part of that collaboration. In June 2019, we expanded our collaboration and entered into a strategic collaboration and license agreement for the development and commercialization of products for the treatment of DMD and DM1.

*ViaCyte.* We entered into the ViaCyte Collaboration Agreement in September 2018 with ViaCyte to pursue 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.

*Bayer.* In the fourth quarter of 2019, we entered into a series of transactions, or the Bayer Transaction, pursuant to which we and Bayer terminated our 2015 agreement, which created the joint venture, Casebia, 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. In connection thereto, Casebia became a wholly-owned subsidiary of ours. We and Bayer also entered into a new option agreement pursuant to which Bayer has an option to co-develop and co-commercialize two products for the diagnosis, treatment or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders for a specified period of time, or, under certain circumstances, exclusively license such optioned products.

Refer to Note 7 of the notes to our consolidated financial statements included in this Annual Report on Form 10-K for a description of the key terms of our arrangements with Vertex, ViaCyte and Bayer.

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 share issuances, convertible loans and collaboration agreements with strategic partners.

All of our revenue to date has been collaboration revenue. We were profitable for the year ended December 31, 2019 due to collaboration revenue from Vertex and Casebia, but we do not expect to sustain our profitability in future years. With the exception of the year ended December 31, 2019, we have incurred significant net operating losses each year since our inception and expect to continue to incur net operating losses for the foreseeable future. As of December 31, 2019, we had \$943.8 million in cash and cash equivalents and an accumulated deficit of \$224.7 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.

## 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, 2019, 2018 and 2017, we recognized \$289.6 million, \$3.1 million and \$41.0 million, respectively, of revenue related to our collaboration agreements with Vertex, as well as certain arrangements with Casebia prior to the Bayer Transaction. 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 IND-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 or the subsequent commercialization of any product candidates we may successfully 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, as well as certain arrangements with Casebia prior to the Bayer Transaction, 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 our research and development costs to increase significantly for the foreseeable future as our current development programs progress, new programs are added and as we continue to prepare regulatory filings. These increases will likely include the costs related to the implementation and expansion of clinical trial sites and related patient enrollment, monitoring, program management and manufacturing expenses for current and future clinical trials. In addition, we expect that our research and development expenses will increase in future periods as we incur additional costs in connection with research and development activities under our collaboration with ViaCyte.

### ***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. In addition, we anticipate increased expenses related to the reimbursements of third-party patent related expenses in connection with certain of our in-licensed intellectual property.

### ***Other income (expense), net***

Other income (expense), net consists primarily of interest income earned on investments, the gain resulting from the consolidation of Casebia following the Bayer Transaction and the loss from equity method investment from stock-based compensation awards granted to employees of Casebia, prior to consolidation.

## 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*

Effective January 1, 2018, we adopted Accounting Standards Codification Topic 606, *Revenue from Contracts with Customers*, or ASC 606, using the modified retrospective transition method. The adoption of this guidance did not have a significant impact on our consolidated financial statements.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases and collaboration arrangements. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps:

#### *1) Identify the contract with the customer*

A contract with a customer exists when (i) we enter 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) we determine that collection of substantially all consideration for goods and services that are transferred is probable based on the customer's intent and ability to pay the promised consideration.

#### *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, we 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 we will be entitled in exchange for transferring goods and services to the customer. To the extent the transaction price includes variable consideration, such as research, development, regulatory and commercial milestones, we determine if it is probable that we will receive such amounts and there is no risk of a significant revenue reversal. When we cannot conclude that receipt of such amounts is probable, we constrain the related variable consideration resulting in its exclusion from transaction consideration. In determining the portion of the transaction consideration to be constrained, we consider the probability and uncertainty that the related research, developmental, regulatory and commercial milestones will be achieved given the nature of research and clinical development and the stage of the underlying programs. This assessment is performed at each reporting period. In making this evaluation, we consider both internal and external information available, including information from industry publications and other relevant factors. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the period.

#### *4) Allocate the transaction consideration to performance obligations in the contract*

If the contract contains a single performance obligation, the entire transaction consideration is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction consideration to each performance obligation on a relative standalone selling price basis unless the transaction consideration 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. In determining these estimated standalone selling prices, we make a number of significant judgements including, for licenses, management's assumptions regarding probability weighted projected discounted cash flows for each of the collaboration development programs. The estimated standalone selling prices are sensitive to changes in assumptions, such as probabilities of scientific success, discount rate and certain assumptions that form the basis of forecasted cash flows. In developing these assumptions, management considers both internal and external information available, including information from other guideline companies within the same industry and other relevant factors. Changes to these assumptions can have a material effect on the allocation of the transaction consideration to performance obligations, as well as the amount and timing of revenue recognized.

#### *5) Recognize revenue when or as we satisfy a performance obligation*

We satisfy performance obligations over time or at a point in time, depending on the nature of the performance obligation. Revenue is recognized over time if the customer simultaneously receives and consumes the benefits provided by the entity's performance, the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or 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.

### ***Collaboration Arrangements***

We record the elements of our collaboration agreements that represent joint operating activities in accordance with ASC 808, *Collaborative arrangements*, or 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.

We evaluate 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.

### ***Accrued research and development expenses***

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

- CROs in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to development, manufacturing and distribution of clinical trial materials.

We base our expenses related to clinical studies on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical study milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period and adjust accordingly.

### ***Variable Interest Entities***

We review each legal entity formed by parties related to us to determine whether or not the entity is a variable interest entity, or VIE, in accordance with 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 ASC Topic 805, *Business Combinations*, on the date we become the primary beneficiary.

The Company determined that Casebia was a VIE and concluded that it was not the primary beneficiary of the VIE prior to December 13, 2019. As such, the Company did not consolidate Casebia's results into the consolidated financial statements prior to December 13, 2019. Instead, the Company accounted for its 50% investment in Casebia under the equity method. On December 13, 2019, Casebia became a fully-owned subsidiary and, as a result, the Company consolidated Casebia's financial results from that date forward.

### ***Equity-Based Compensation***

Our share-based compensation programs grant awards that have included stock options, restricted stock units and restricted stock awards. Grants are awarded to employees and non-employees, including directors.

We account for our stock-based compensation awards in accordance with ASC Topic 718, *Compensation—Stock Compensation*, or ASC 718. ASC 718 requires all stock-based payments to employees and non-employee directors, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive loss based on their fair values. We use the Black-Scholes option pricing model to determine the fair value of options granted.

We account for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

Prior to the adoption of ASU No. 2018-07, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*, or ASU 2018-07, on July 1, 2018, the measurement date for non-employee awards was generally the date the services were completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After adoption of ASU 2018-07, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award.

Our stock-based awards are subject to service or performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees and non-employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

We expense restricted stock unit awards to employees based on the fair value of the award on a straight-line basis over the associated service period of the award.

We estimate the fair value of our option awards to employees, directors and non-employees using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. Due to the lack of complete company-specific historical and implied volatility data for the full expected term of the stock-based awards, we base our estimate of expected volatility on a representative group of publicly traded companies in addition to our own volatility data. For these analyses, we selected companies with comparable characteristics to our own, including enterprise value, risk profiles, position within the industry and with historical share price information sufficient to meet the expected life of the stock-based awards. We compute historical volatility data using the daily closing prices for the selected companies' shares during the equivalent period of the calculated expected term of the stock-based awards. We will continue to apply this process until a sufficient amount of historical information regarding the volatility of our own stock price becomes available. We have estimated the expected term of our employee stock options using the "simplified" method, whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the option due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. We have never paid, and do not expect to pay, dividends in the foreseeable future.

## Recent Accounting Pronouncements

Refer to Note 2 of the notes to our consolidated financial statements included in this Annual Report on Form 10-K for a discussion of recent accounting pronouncements.

## Results of Operations

### *Comparison of Years Ended December 31, 2019 and 2018*

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018, together with the dollar change in those items:

	Years Ended December 31, 2019	2018 (in thousands)	Period-to- Period Change
Collaboration revenue	\$ 289,590	\$ 3,124	\$ 286,466
Operating expenses:			
Research and development	179,362	113,773	65,589
General and administrative	63,488	48,294	15,194
Total operating expenses	242,850	162,067	80,783
Income (loss) from operations	46,740	(158,943)	205,683
Other income (expense), net	20,566	(5,485)	26,051
Net income (loss) before income taxes	67,306	(164,428)	231,734
Provision for income taxes	(448)	(553)	105
Net income (loss)	<u>\$ 66,858</u>	<u>\$ (164,981)</u>	<u>\$ 231,839</u>

### *Collaboration Revenue*

Collaboration revenue was \$289.6 million for the year ended December 31, 2019, compared to \$3.1 million for the year ended December 31, 2018. The increase of \$286.5 million was primarily due to recognition of \$289.1 million in revenue in 2019 in connection with the collaboration agreements with Vertex. Refer to Note 7 of the notes to our consolidated financial statements included in this Annual Report on Form 10-K for a description of revenue recognized related to Vertex.

### *Research and Development Expenses*

Research and development expenses were \$179.4 million for the year ended December 31, 2019, compared to \$113.8 million for the year ended December 31, 2018. The increase of \$65.6 million was primarily attributable to the following:

- \$24.4 million of increased employee compensation, benefit and other headcount related expenses, of which \$5.7 million is increased stock-based compensation expense, primarily due to an increase in headcount to support advancing programs and research;
- \$28.3 million of increased variable research and development costs; and
- \$12.3 million of increased facility-related expenses.

### General and Administrative Expenses

General and administrative expenses were \$63.5 million for the year ended December 31, 2019, compared to \$48.3 million for the year ended December 31, 2018. The increase of \$15.2 million was primarily attributable to the following:

- \$8.2 million of increased employee compensation, benefit and other headcount related expenses, of which \$3.4 million is increased stock-based compensation expense, primarily due to an increase in headcount to support overall growth;
- \$2.2 million of increased intellectual property costs;
- \$2.2 million of increased professional services costs; and,
- \$1.6 million of increased facility-related expenses.

### Other income (expense), net

Other income, net, was \$20.6 million for the year ended December 31, 2019, compared to \$5.5 million in other expense, net, for the year ended December 31, 2018. Other income, net for the year ended December 31, 2019 consisted of interest income of \$10.1 million, a \$16.0 million gain resulting from the consolidation of Casebia following the Bayer Transaction, offset by \$5.5 million in losses from equity method investment from stock-based compensation awards granted to employees of Casebia prior to the Bayer Transaction. Other expense, net, for the year ended December 31, 2018 consisted of interest income of \$0.2 million, offset by \$2.5 million of losses from equity method investment from stock-based compensation awards granted to employees of Casebia and \$1.2 million related to the change in fair value of the derivative liability issued under the ViaCyte Collaboration Agreement.

### 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-
	2018	2017	Period Change
	(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	<u>162,067</u>	<u>105,645</u>	<u>56,422</u>
Loss from operations	(158,943)	(64,648)	(94,295)
Other (expense) income, net	(5,485)	(1,960)	(3,525)
Net loss before provision for income taxes	(164,428)	(66,608)	(97,820)
Provision for income taxes	(553)	(1,749)	1,196
Net loss	<u>\$ (164,981)</u>	<u>\$ (68,357)</u>	<u>\$ (96,624)</u>

### 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:

- \$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:

- \$7.4 million of stock-based compensation costs;
- \$3.5 million in intellectual property costs;
- \$2.8 million in employee-related costs; offset by,
- \$1.2 million of decreased professional, consulting and facilities costs.

#### *Other Income (Expense), Net*

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.

### **Liquidity and Capital Resources**

#### *Sources of Liquidity*

As of December 31, 2019, we had cash and cash equivalents of approximately \$943.8 million, of which \$891.0 million was held outside of the United States.

With our cash on hand as of December 31, 2019, we expect cash and cash equivalents to be sufficient to fund our current operating plan through at least the next 24 months.

We have predominantly incurred losses and cumulative negative cash flows from operations since our inception, and as of December 31, 2019, we had an accumulated deficit of \$224.7 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.

Since our initial public offering, we have primarily financed our operations through common share issuances (as outlined below) and collaboration agreements with strategic partners. Recent sources of equity financing include:

- In January 2018, we completed an underwritten public offering of 5.7 million common shares (inclusive of shares sold pursuant to an over-allotment option granted to the underwriters in connection with the offering), which were sold at a price of \$22.75 per share. This offering resulted in net proceeds to us of \$122.6 million, which were net of equity issuance costs of \$8.2 million.
- In September 2018, we completed an underwritten public offering of 4.2 million common shares, which were sold at a price to the public of \$47.50 per share. This offering resulted in net proceeds to us of \$184.5 million, which was net of equity issuance costs of \$15.5 million.
- In the first quarter of 2019, we began to issue and sell securities under an Open Market Sale Agreement<sup>SM</sup> entered into with Jefferies LLC, or Jefferies, in August 2018, or the 2018 ATM, under which we may offer and sell, from time to time, common shares having aggregate gross proceeds of up to \$125.0 million. During the year ended December 31, 2019, we issued and sold an aggregate of 2.8 million common shares at an average price of \$44.38 per share for aggregate net proceeds of \$120.6 million, which were net of equity issuance costs of \$4.4 million.
- In November 2019, we sold 4.9 million common shares through an underwritten public offering (inclusive of shares sold pursuant to the exercise of the option to purchase additional shares granted to the underwriters in connection with the offering) at a price of \$64.50 per share for aggregate net proceeds of \$294.4 million, which were net of equity issuance costs of \$20.7 million.



In addition, in August 2019, following the termination of the 2018 ATM by its terms, we entered into a new Open Market Sale Agreement<sup>SM</sup> with Jefferies, or the 2019 ATM, under which we may offer and sell, from time to time, common shares having aggregate gross proceeds of up to \$200.0 million. We have not yet issued or sold any securities under the 2019 ATM.

## Sources of Liquidity

### Cash Flows

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

	Years Ended December 31,		
	2019	2018	2017
	(in thousands)		
Net cash provided by (used in) operating activities	\$ 56,677	\$ (96,239)	\$ (70,093)
Net cash provided by (used in) investing activities	1,325	(2,773)	(8,314)
Net cash provided by financing activities	430,983	315,934	2,608
Effect of exchange rate changes on cash	15	(22)	41
Increase (decrease) in cash and restricted cash	<u>\$ 489,000</u>	<u>\$ 216,900</u>	<u>\$ (75,758)</u>

### Operating Activities

Net cash provided by operating activities was \$56.7 million for the year ended December 31, 2019 and primarily consisted of net income of \$66.9 million adjusted for non-cash items (including equity-based compensation expense of \$44.1 million, depreciation and amortization expense of \$4.7 million, and a loss from equity method investment of \$5.5 million, offset by a gain from our equity method investment in Casebia of \$16.0 million as a result of the Bayer Transaction), reduced by an increase in prepaid expenses and other current assets of \$32.6 million, primarily driven by contract assets resulting from the Vertex collaborations, and a decrease in deferred revenue of \$45.1 million, primarily resulting from the exercise of options under the Vertex collaboration, offset by an increase of \$25.0 million in other liabilities, net, primarily related to research obligations as a result of the Bayer Transaction and an increase in accounts payable and accrued expenses of \$5.0 million.

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.

### Investing Activities

Net cash provided by investing activities for the year ended December 31, 2019 was \$1.3 million and consisted of \$8.0 million in net cash and restricted cash acquired from Casebia in connection with the Bayer Transaction, offset by \$6.7 million 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, 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, Massachusetts office.

### *Financing Activities*

Net cash provided by financing activities for the year ended December 31, 2019 was \$430.9 million and consisted of net proceeds of \$415.0 million from the issuance of common shares and net proceeds of \$15.9 million from stock option exercise.

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.

### *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 and 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 financings, 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 our collaboration with Vertex. Except for this source 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 collaborations 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.

### *Contractual Obligations*

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2019 (in thousands):

	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease and sublease obligations - commenced	\$ 70,209	\$ 13,963	\$ 21,991	\$ 18,577	\$ 15,678
Operating lease obligations - not yet commenced	\$ 21,197	\$ 3,317	\$ 7,400	\$ 7,400	\$ 3,080

#### *Operating lease and sublease obligations - commenced*

Our operating lease obligations primarily consist of lease payments on our research and office facilities in Cambridge, Massachusetts, which are described in further detail in Note 5 of our consolidated financial statements included in this Annual Report on Form 10-K.

#### *Operating lease obligations – not yet commenced*

In November 2019, we, together with one of our partners, entered into a commitment with a clinical manufacturing organization under a lease agreement, which is described in further detail in Note 5 of the consolidated financial statements included in this Annual Report on Form 10-K. The amounts in the table represent the amounts owed from us to the manufacturing organization and our partner has agreed to reimburse us for 50% of the amounts paid under this agreement.

In December 2019, as part of the Bayer Transaction, we and Bayer entered into an option agreement, under which, among other things, we committed to invest a specified amount in certain research and development activities as described in further detail in Note 7 of our consolidated financial statements included in this Annual Report on Form 10-K.

Under the Invention Management Agreement signed on December 15, 2016, we are 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, and Caribou's licensee Intellia Therapeutics. Because such costs are not quantifiable at this time, they have not been included in the above table.

In the normal course of business, we enter into agreements with contract research organizations for clinical trials and clinical supply manufacturing and with vendors for pre-clinical research studies and other services and products for operating purposes. We have not included these payments in the table of contractual obligations above since the contracts are generally cancelable at any time by us upon less than 180 days' prior written notice. Certain of these agreements require us to pay milestones to such third parties upon achievement of certain development, regulatory or commercial milestones as further described in Note 6 of our consolidated financial statements included in this Annual Report on Form 10-K. Amounts related to contingent milestone payments are not considered contractual obligations as they are contingent on the successful achievement of certain development, regulatory approval and commercial milestones, which may not be achieved.

We also have obligations to make future payments to third parties that become due and payable on the achievement of certain milestones, including future payments to third parties with whom we have entered into research, development and commercialization agreements. We have not included these commitments on our balance sheet or in the table above because the achievement and timing of these milestones is not fixed and determinable.

### **Off-Balance Sheet Arrangements**

As of December 31, 2019, we do not have any off-balance sheet arrangements, as defined under applicable SEC rules.

**Item 7A. Quantitative and Qualitative Disclosures About Market Risk.***Interest Rate Sensitivity*

Cash and cash equivalents were held primarily in cash deposits and money market funds. The fair value of our cash and cash equivalents would not be significantly affected by either an increase or decrease in interest rates due mainly to the short-term nature of these instruments.

*Foreign Currency Exchange Rate 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.

**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**

Our chief executive officer and chief financial officer, after evaluating the effectiveness of our 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, our disclosure controls and procedures were effective. In designing and evaluating the disclosure controls and procedures, our 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 our 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**

Management 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, our principal executive and principal financial officers and effected by our Board of Directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Our 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 our transactions and dispositions of the assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the 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.

Our management assessed the effectiveness of the Company's internal control over financial reporting as of December 31, 2019. 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, our management has concluded that, as of December 31, 2019, the Company's internal control over financial reporting is effective based on those criteria.

Our independent registered public accounting firm, Ernst & Young LLP, issued an attestation report on our internal control over financial reporting. See below.

### **Changes in Internal Control Over Financial Reporting**

There have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, during the fourth quarter of 2019 that have materially affected, or are 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, 2019, 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, 2019, based on the COSO criteria.

We also have 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, 2019 and 2018, the related consolidated statements of operations and comprehensive income (loss), shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2019, and the related notes and our report dated February 12, 2020 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 Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

### Definition and Limitations of Internal Control Over Financial Reporting

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

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

/s/ Ernst & Young LLP

Boston, Massachusetts  
February 12, 2020

**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 2020 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2019.

### **Item 11. Executive Compensation.**

The information required by this item is incorporated by reference to our Proxy Statement for our 2020 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2019.

### **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 2020 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2019.

### **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 2020 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2019.

### **Item 14. Principal Accounting Fees and Services.**

The information required by this item is incorporated by reference to our Proxy Statement for our 2020 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2019.



## 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.

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)(2) 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*	Amended and Restated Articles of Association of CRISPR Therapeutics AG, dated December 2, 2019.
4.1*	Description of Capital Shares
10.1†	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).
10.2†	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).
10.3†	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).
10.4†	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).
10.5	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).
10.6	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).
10.7#	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).
10.8#	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).
10.9#	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).

Exhibit Number	Description
10.10#	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).
10.11#	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).
10.12#	Employment Agreement, dated January 2, 2019, by and between CRISPR Therapeutics, Inc. and Lawrence Klein (incorporated herein by reference to Exhibit 10.16 to the Company's Annual Report on Form 10-K filed on February 25, 2019).
10.13#	Mandate Agreement, dated December 27, 2019, by and between CRISPR Therapeutics AG and Oriolus Consulting LLC (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K filed on December 27, 2019).
10.14#	Termination Agreement, dated December 27, 2019, 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 27, 2019).
10.15#	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).
10.16#	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).
10.16.1#	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).
10.16.2#	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).
10.16.3#	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).
10.16.4#	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).
10.16.5#	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).
10.16.6#	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).
10.17#	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).
10.17.1#	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).
10.17.2#	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).
10.17.3#	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).

Exhibit Number	Description
10.17.4#	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).
10.17.5#	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).
10.17.6#	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).
10.18#	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).
10.19	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).
10.20†	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).
10.21†	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).
10.22†	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).
10.23#	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).
10.24†	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).
10.25†*	Amendment No. 1 to Research Collaboration Agreement by and between CRISPR Therapeutics AG and ViaCyte, Inc., dated as of April 30, 2019.
10.26†	Amendment No. 2 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 June 6, 2019 (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on July 29, 2019).
10.27†	Strategic Collaboration and License Agreement dated June 6, 2019, between CRISPR Therapeutics AG and Vertex Pharmaceuticals Incorporated (incorporated herein by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q filed on July 29, 2019).
10.28†*	Amendment No. 2 to Research Collaboration Agreement by and between CRISPR Therapeutics AG and ViaCyte, Inc., dated as of October 21, 2019.

Exhibit Number	Description
10.29†*	Joint Venture Termination Agreement, dated December 13, 2019, among Bayer Healthcare LLC (and certain affiliates of Bayer Healthcare LLC for purposes of Article II), CRISPR Therapeutics AG (and certain subsidiaries of CRISPR Therapeutics AG for purposes of Article II), and Casebia Therapeutics Limited Liability Partnership.
10.30†*	Retirement Agreement, dated December 13, 2019, among Casebia Therapeutics Limited Liability Partnership, Bayer HealthCare LLC, CRISPR Therapeutics AG and CRISPR Therapeutics, Inc.
10.31†*	Option Agreement, dated December 13, 2019, between CRISPR Therapeutics AG and Bayer HealthCare LLC.
10.32†*	Assignment of Sublease and Sub-Sublease, dated December 13, 2019, between Casebia Therapeutics LLC and CRISPR Therapeutics, Inc.
21.1*	Subsidiaries of the Registrant
23.1*	Consent of Ernst & Young 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	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

\* Filed herewith.

+ Furnished herewith.

† Confidential portions of this exhibit have been omitted.

# 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.





## CRISPR Therapeutics AG

<b>Index to Consolidated Financial Statements</b>	<b>Pages</b>
Report of Independent Registered Public Accounting Firm	F-2
Consolidated Balance Sheets	F-5
Consolidated Statements of Operations and Comprehensive Income (Loss)	F-6
Consolidated Statements of Equity	F-7
Consolidated Statements of Cash Flows	F-8
Notes to Consolidated Financial Statements	F-9

## 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, 2019 and 2018, the related consolidated statements of operations and comprehensive income (loss), shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2019, and the related notes (collectively referred to as the "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, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with 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, 2019, 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 12, 2020 expressed an unqualified opinion thereon.

### Adoption of ASU No. 2016-02, "Leases"

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, *Leases* (Topic 842), and the related amendments.

### 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 include examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.



## Critical Audit Matters

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

### *Estimation of Variable Consideration for ongoing Collaboration Agreements*

#### *Description of the Matter*

As discussed in Note 7 to the consolidated financial statements, the Company has multiple ongoing collaboration agreements which include rights to future payments totaling up to \$2.06 billion as of December 31, 2019 that are payable upon the achievement of various developmental, regulatory and commercial milestones related to certain programs under development. These future payments represent variable consideration that is included in the transaction price for these collaboration agreements to the extent that the Company determines it is probable that a significant revenue reversal of cumulative revenue recognized under the contract will not occur. When the Company cannot conclude that it is probable that a significant revenue reversal of cumulative revenue under the contract will not occur, the Company constrains the related variable consideration resulting in its exclusion from the transaction price. The Company's estimation of variable consideration to be constrained impacts the reported amounts of revenue and deferred revenue within the consolidated financial statements.

In determining the portion of the transaction price to be constrained, management considers the probability and uncertainty of whether the related developmental, regulatory and commercial milestones will be achieved given the nature of clinical development and the stage of the underlying programs. This assessment is performed at each reporting period. In making this evaluation, management considers both internal and external information available including information from industry publications, the stage of development of the underlying programs and other relevant factors. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the financial reporting period. As a result, auditing the accounting for the application of constraint to variable consideration required especially complex auditor judgement.

#### *How We Addressed the Matter in Our Audit*

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's revenue recognition process. For example, we tested controls over management's estimation of the total transaction price for its collaboration agreements including those related to the application of constraint to variable consideration associated with future developmental, regulatory and commercial milestones.

To audit the Company's judgements related to the application of constraint to variable consideration, we performed audit procedures that included, among others, evaluating the Company's judgements related to the probability of achieving the related future developmental, regulatory and commercial milestones. To evaluate the Company's estimated probability of achieving developmental, regulatory and commercial milestones, we considered the nature of clinical development and the stage of development of the underlying programs in relation to relevant external data and compared the probabilities of achieving the milestones to current industry trends and available information from other guideline companies within the same industry and other relevant factors. We also discussed the probability of achieving the milestones in relation to each program's phase of development with the Company's research and development managers.

## ***Revenue Recognition for Collaboration Agreements with Vertex Pharmaceuticals Incorporated***

### ***Description of the Matter***

As discussed in Note 7 to the consolidated financial statements, on July 23, 2019 the Company entered into a series of agreements with Vertex Pharmaceuticals Inc., collectively referred to as the “2019 Collaboration Agreements”, which resulted in the recognition of \$289.6 million of revenue for the year ended December 31, 2019 and \$12.7 million of deferred revenue as of December 31, 2019.

Accounting for the 2019 Collaboration Agreements required the Company to make a number of significant judgements, including the estimation of the standalone selling price of each identified performance obligation. The estimates of the standalone selling price for certain performance obligations reflect management’s assumptions regarding probability weighted projected discounted cash flows for each of the underlying programs. The estimates of standalone selling prices were sensitive to changes in assumptions such as the probability of scientific success of the programs, discount rate, and certain assumptions that form the basis of the forecasted cash flows (e.g., price per patient). In developing these assumptions, management considered both internal and external information available including information from other guideline companies within the same industry and other relevant factors. Changes to these assumptions can have a material effect on the allocation of the transaction price to the performance obligations as well as the amount and timing of revenue recognized. As a result, auditing the estimates of standalone selling price for certain performance obligations required especially complex auditor judgement.

### ***How We Addressed the Matter in Our Audit***

We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company’s revenue recognition process. For example, we tested controls over management’s process to determine the significant assumptions described above with respect to the estimation of the standalone selling price of certain performance obligations.

To audit the Company’s revenue recognition related to the 2019 Collaboration Agreements, we performed audit procedures that included, among others, evaluating management’s estimates of the standalone selling price of certain performance obligations. For example, we evaluated the probability weighted projected discounted cash flow assumptions used by the Company in developing the estimates of standalone selling price by comparing the significant assumptions described above to current industry trends using available information from other guideline companies within the same industry and other relevant factors. We also performed a sensitivity analysis of the significant assumptions to evaluate the impact that the change in the estimated standalone selling price of certain performance obligations resulting from changes in the significant assumptions would have on the allocation of transaction price to each performance obligation, as well as revenue recognized during the period. We involved our valuation professionals to assist in the assessment of the estimation methodology and the significant assumptions used in determining the estimated standalone selling price of certain performance obligations.

/s/ Ernst & Young LLP

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

Boston, Massachusetts

February 12, 2020

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

	December 31,	
	2019	2018
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 943,771	\$ 456,649
Accounts receivable, including related party amounts of \$0 and \$88 as of December 31, 2019 and 2018, respectively	99	88
Prepaid expenses and other current assets, including related party amounts of \$0 and \$3,417 as of December 31, 2019 and 2018, respectively	43,677	9,658
Total current assets	987,547	466,395
Property and equipment, net	31,330	18,500
Intangible assets, net	235	289
Restricted cash	5,041	3,163
Operating lease assets	41,502	—
Other non-current assets	1,097	669
Total assets	<u>\$ 1,066,752</u>	<u>\$ 489,016</u>
<b>Liabilities and Shareholders' Equity</b>		
Current liabilities:		
Accounts payable	\$ 5,944	\$ 5,069
Accrued expenses, including related party amounts of \$0 and \$1,700 as of December 31, 2019 and 2018, respectively	30,180	20,852
Deferred revenue current, including related party amounts of \$0 and \$102 as of December 31, 2019 and 2018, respectively	960	102
Accrued tax liabilities	583	402
Deferred rent	—	1,202
Operating lease liabilities	8,489	—
Other current liabilities	10,950	119
Total current liabilities	57,106	27,746
Deferred revenue, including related party amounts of \$0 and \$57,780 as of December 31, 2019 and 2018, respectively	11,776	57,780
Deferred rent non-current	—	11,052
Operating lease liabilities, net of current portion	44,050	—
Other non-current liabilities	14,395	243
Total liabilities	127,327	96,821
Commitments and contingencies (Note 6)		
Shareholders' equity:		
Common shares, CHF 0.03 par value, 103,901,006 and 90,343,803 shares authorized at December 31, 2019 and 2018, respectively, 61,034,025 and 52,160,798 shares issued at December 31, 2019 and 2018, respectively, 60,783,799 and 51,852,862 shares outstanding at December 31, 2019 and 2018, respectively.	1,847	1,584
Treasury shares, at cost, 250,226 and 307,936 shares at December 31, 2019 and 2018, respectively	(63)	(57)
Additional paid-in capital	1,162,345	682,245
Accumulated deficit	(224,711)	(291,569)
Accumulated other comprehensive income (loss)	7	(8)
Total shareholders' equity	939,425	392,195
Total liabilities and shareholders' equity	<u>\$ 1,066,752</u>	<u>\$ 489,016</u>

*See accompanying notes to these consolidated financial statements.*

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

	Years Ended December 31,		
	2019	2018	2017
Collaboration revenue (1)	\$ 289,590	\$ 3,124	\$ 40,997
Operating expenses:			
Research and development (2)	179,362	113,773	69,800
General and administrative	63,488	48,294	35,845
Total operating expenses	<u>242,850</u>	<u>162,067</u>	<u>105,645</u>
Income (loss) from operations	46,740	(158,943)	(64,648)
Other income (expense):			
Loss from equity method investment	(5,467)	(4,275)	(1,763)
Other income (expense), net	26,033	(1,210)	(197)
Total other income (expense), net	20,566	(5,485)	(1,960)
Net income (loss) before income taxes	67,306	(164,428)	(66,608)
Provision for income taxes	(448)	(553)	(1,749)
Net income (loss)	66,858	(164,981)	(68,357)
Foreign currency translation adjustment	15	(22)	40
Comprehensive income (loss)	<u>\$ 66,873</u>	<u>\$ (165,003)</u>	<u>\$ (68,317)</u>
Net income (loss) per share attributable to common shareholders— basic	<u>\$ 1.23</u>	<u>\$ (3.44)</u>	<u>\$ (1.71)</u>
Weighted-average common shares outstanding used in net income (loss) per share attributable to common shareholders—basic	<u>54,392,304</u>	<u>47,964,368</u>	<u>40,057,365</u>
Net income (loss) per share attributable to common shareholders— diluted	<u>\$ 1.17</u>	<u>\$ (3.44)</u>	<u>\$ (1.71)</u>
Weighted-average common shares outstanding used in net income (loss) per share attributable to common shareholders—diluted	<u>56,932,798</u>	<u>47,964,368</u>	<u>40,057,365</u>
(1) Including the following amounts of revenue from a related party, see Note 7	\$ 746	\$ 3,124	\$ 4,760
(2) Including the following amounts of research and development from a related party, see Note 7	\$ 14,459	\$ 23,982	\$ 4,523

*See accompanying notes to these consolidated financial statements.*

**CRISPR Therapeutics AG**  
**Consolidated Statements of Shareholders' Equity**  
(In thousands, except share and per share data)

	Common Shares		Treasury Shares		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total CRISPR Therapeutics AG Shareholders' Equity (Deficit)
	Shares	CHF 0.03 Par Value	Shares	Amount, at cost				
<b>Balance at December 31, 2016</b>	39,719,434	\$ 1,216	444,873	\$ —	288,739	\$ (57,083)	\$ (26)	\$ 232,846
Vesting of restricted shares	33,519	—	—	—	58	—	—	59
Exercise of vested options	839,295	23	—	—	2,585	—	—	2,608
Stock-based compensation expense	—	—	—	—	20,636	—	—	20,636
Other comprehensive income	—	—	—	—	—	—	40	40
Net loss	—	—	—	—	—	(68,357)	—	(68,357)
<b>Balance at December 31, 2017</b>	40,592,248	\$ 1,240	444,873	\$ —	312,018	\$ (125,440)	\$ 14	\$ 187,832
Cumulative effect of ASC 606 adoption	—	—	—	—	—	(1,148)	—	(1,148)
Issuance of common shares, net of issuance costs of \$23.8 million	9,960,526	311	—	—	306,742	—	—	307,053
Vesting of restricted shares	38,761	1	—	—	112	—	—	113
Exercise of vested options, net of issuance costs of \$0.4 million	946,131	26	(36,253)	—	8,537	—	—	8,563
Repurchase of treasury shares	(64,952)	—	64,952	(57)	—	—	—	(57)
Issuance of shares to ViaCyte	380,148	6	(165,656)	—	15,576	—	—	15,582
Stock-based compensation expense	—	—	—	—	39,260	—	—	39,260
Other comprehensive loss	—	—	—	—	—	(164,981)	(22)	(22)
Net loss	—	—	—	—	—	(164,981)	—	(164,981)
<b>Balance at December 31, 2018</b>	51,852,862	\$ 1,584	307,936	\$ (57)	682,245	\$ (291,569)	\$ (8)	\$ 392,195
Issuance of common shares, net of issuance costs of \$25.1 million	7,704,068	230	(47,297)	—	414,559	—	—	414,789
Vesting of restricted shares	68,009	2	—	—	41	—	—	43
Exercise of vested options, net of issuance costs of \$0.3 million	1,158,860	31	(10,413)	(6)	15,976	—	—	16,001
Stock-based compensation expense	—	—	—	—	49,524	—	—	49,524
Other comprehensive income	—	—	—	—	—	—	15	15
Net income	—	—	—	—	—	—	66,858	66,858
<b>Balance at December 31, 2019</b>	60,783,799	\$ 1,847	250,226	\$ (63)	1,162,345	\$ (224,711)	\$ 7	\$ 939,425

*See accompanying notes to these consolidated financial statements.*

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

	Years Ended December 31,		
	2019	2018	2017
<b>Operating activities</b>			
Net income (loss)	\$ 66,858	\$ (164,981)	\$ (68,357)
Reconciliation of net loss to net cash used in operating activities:			
Depreciation and amortization	4,725	3,519	3,024
Equity-based compensation	44,057	34,985	18,873
Loss from equity method investment in Casebia	5,467	4,275	1,763
Non-cash expense related to ViaCyte transaction	—	15,582	—
Gain from consolidation of Casebia	(16,000)	—	—
Other income, non-cash	—	(169)	(9)
Changes in:			
Accounts receivable	(11)	2,538	531
Prepaid expenses and other assets	(32,618)	(3,342)	(4,117)
Accounts payable and accrued expenses	5,025	12,110	(831)
Deferred revenue	(45,146)	(296)	(20,718)
Deferred rent	—	(709)	(522)
Operating lease assets and liabilities	(663)	—	—
Other liabilities, net	24,983	249	270
Net cash provided by (used in) operating activities	56,677	(96,239)	(70,093)
<b>Investing activities</b>			
Purchase of property and equipment	(6,684)	(2,773)	(7,814)
Net cash and restricted cash received in connection with the acquisition of Casebia	8,009	—	—
Purchase of available for sale debt security	—	—	(500)
Net cash provided by (used in) investing activities	1,325	(2,773)	(8,314)
<b>Financing activities</b>			
Proceeds from issuance of common shares, net of issuance costs	415,019	307,053	—
Proceeds from exercise of options, net of issuance costs	15,964	8,938	2,608
Repurchase of treasury shares	—	(57)	—
Net cash provided by financing activities	430,983	315,934	2,608
Effect of exchange rate changes on cash	15	(22)	41
Increase in cash	489,000	216,900	(75,758)
Cash, cash equivalents and restricted cash, beginning of period	459,812	242,912	318,670
Cash, cash equivalents and restricted cash, end of period	\$ 948,812	\$ 459,812	\$ 242,912
<b>Supplemental disclosure of non-cash investing and financing activities</b>			
Property and equipment purchases in accounts payable and accrued expenses	\$ 1,811	\$ 334	—
Stock option issuance costs included in accrued expenses	\$ 295	\$ 375	—
Costs for proposed supplemental offering in accounts payable and accrued expenses	\$ —	\$ —	\$ 290
<b>Reconciliation to amounts within the consolidated balance sheets</b>			
	As of December 31,		
	2019	2018	2017
Cash and cash equivalents	943,771	456,649	239,758
Restricted Cash	5,041	3,163	3,154
Total	\$ 948,812	\$ 459,812	\$ 242,912

*See accompanying notes to these consolidated financial statements.*

# CRISPR Therapeutics AG

## Notes to Consolidated Financial Statements

### 1. Organization and Operations

CRISPR Therapeutics AG (“CRISPR” or the “Company”) was incorporated on October 31, 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 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 \$224.7 million as of December 31, 2019 and has financed its operations to date from a series of preferred shares and convertible loan issuances, proceeds obtained from its initial public offering, subsequent public offerings of its common shares, as well as upfront fees and milestones 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.

As of December 31, 2019, the Company had cash and cash equivalents of \$943.8 million. While the Company had net income of \$66.9 million for the year ended December 31, 2019, the Company has a history of recurring losses and expects to continue to incur losses for the foreseeable future. The Company expects its cash and cash equivalents will be sufficient to fund current planned operations for at least the next twenty-four months.

### 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 the Company and its wholly-owned subsidiaries as of December 31, 2019. 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.

Prior to December 13, 2019, the Company accounted for its 50% investment in Casebia Therapeutics, Limited Liability Partnership (“Casebia”) under the equity method. As described in Note 7, on December 13, 2019, Casebia became a fully-owned subsidiary and, as a result, the Company consolidated Casebia’s financial results from that date forward.

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, revenue recognition, equity-based compensation expense and reported amounts of expenses during the period. Significant estimates in these consolidated financial statements have been made in connection with revenue recognition and equity-based compensation expense. 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.

Certain items in the prior year’s condensed consolidated financial statements have been reclassified to conform to the current presentation. As a result, no subtotals in the prior year condensed consolidated financial statements were impacted.

#### *Segment Information*

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 majority of the Company's operations occur in entities that have the U.S. dollar as their functional currency. Non-U.S. dollar denominated functional currency subsidiaries have assets and liabilities translated into U.S. dollars at rates of exchange in effect at the end of the year. Revenue and expense amounts 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 income (loss)." Net foreign currency exchange transaction gains or losses are included in "Other income (expense), net" on the Company's consolidated statement of operations, the impact of which is not significant.

### ***Cash and Cash Equivalents***

The Company considers all highly liquid investments with maturities of three months or less from the purchase date to be cash equivalents. As of December 31, 2019 and 2018, the Company had \$943.8 million and \$456.6 million in cash equivalents, respectively.

### ***Restricted Cash***

As of December 31, 2019 and 2018, the Company had \$5.0 million and \$3.2 million, respectively, in restricted cash representing letters of credit securing the Company's obligations under certain leased facilities in Cambridge, Massachusetts, as well as certain credit card arrangements. The letters of credit are secured by cash held in a restricted depository account.

### ***Other Receivables***

Other receivables of \$4.1 million and \$3.4 million at December 31, 2019 and 2018, respectively, consists of receivables from Vertex and are included with prepaid and other current assets in the consolidated balance sheet. These amounts represent the balance due from the portion of our arrangement accounted for under ASC 808, *Collaborative Arrangements*. Other receivables are recorded at invoiced amounts due under the Vertex collaboration agreement (see Note 7). Vertex is a creditworthy entity that maintains an ongoing relationship with the Company and 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 has certain financial assets and liabilities recorded at fair value which have been classified as Level 1, 2 or 3 within the fair value hierarchy as described in the accounting standards for fair value measurements:

- 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, 2019 and 2018, approximate fair value, due to the short-term duration of these instruments.



### ***Property and Equipment***

Property and equipment are recorded 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:

<b>Asset</b>	<b>Estimated useful life</b>
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 reviews long-lived assets when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparison of the book values of the assets to 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, which is measured based on the projected discounted future net cash flows arising from the assets.

### ***Revenue Recognition***

Effective January 1, 2018, the Company adopted ASC Topic 606, *Revenue from Contracts with Customers* (“ASC 606”), using the modified retrospective transition 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 adoption of this guidance did not have a significant impact on our consolidated financial statements. The reported results for 2019 and 2018 reflect the application of ASC 606 guidance while the reported results for 2017 were prepared under the guidance of ASC 605, *Revenue Recognition* (“ASC 605”).

In connection with adopting ASC 606, the Company elected a practical expedient and applied ASC 606 only to contracts that were not completed at the date of initial application. In addition, 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.

ASC 606 applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases and collaboration arrangements. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs 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 such as research, development, regulatory and commercial milestones, the Company determines if it is probable that it will receive such amounts and there is no risk of a significant revenue reversal. When the Company cannot conclude that receipt of such amounts is probable, the Company constrains the related variable consideration resulting in its exclusion from transaction consideration. In determining the portion of the transaction consideration to be constrained, the Company considers the probability and uncertainty that the related research, developmental, regulatory and commercial milestones will be achieved given the nature of research and clinical development and the stage of the underlying programs. This assessment is performed at each reporting period. In making this evaluation, the Company considers both internal and external information available, including information from industry publications and other relevant factors. Changes to the constraint of variable consideration can have a material effect on the amount of revenue recognized in the period.

### *4) Allocate the transaction consideration to performance obligations in the contract*

If the contract contains a single performance obligation, the entire transaction consideration is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction consideration to each performance obligation on a relative standalone selling price basis unless the transaction consideration 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. In determining these estimated standalone selling prices, the Company makes a number of significant judgements including, for licenses, management's assumptions regarding probability weighted projected discounted cash flows for each of the collaboration development programs. The estimated standalone selling prices are sensitive to changes in assumptions, such as probabilities of scientific success, discount rate and certain assumptions that form the basis of forecasted cash flows. In developing these assumptions, management considers both internal and external information available, including information from other guideline companies within the same industry and other relevant factors. Changes to these assumptions can have a material effect on the allocation of the transaction consideration to performance obligations, as well as the amount and timing of revenue recognized.

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

The Company satisfies performance obligations over time or at a point in time, depending on the nature of the performance obligation. Revenue is recognized over time if the customer simultaneously receives and consumes the benefits provided by the entity's performance, the entity's performance creates or enhances an asset that the customer controls as the asset is created or enhanced, or 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.

### *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 Company recorded contract assets of \$25.7 million and \$0.0 million as of December 31, 2019 and 2018, respectively. Deferred revenue as of December 31, 2019 and 2018 was \$12.7 million and \$57.8 million. The change in contract assets and deferred revenue is related to the collaboration agreement with Vertex described in Note 7.

### *Collaboration Arrangements*

The Company records the elements of its collaboration agreements that represent joint operating activities in accordance with ASC 808, *Collaborative arrangements* ("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 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 are charged to expense as costs are incurred in performing research and development activities, including salaries and benefits, facilities costs, overhead costs, clinical study and related clinical manufacturing costs, license and milestone fees, contract services and other related costs. Research and development costs, including up-front fees and milestones paid to collaborators, are also expensed as incurred. In circumstances where amounts have been paid in excess of costs incurred, the Company records a prepaid expense. The Company accrues costs for clinical trial activities based upon estimates of the services received and related expenses incurred that have yet to be invoiced by the contract research organizations, clinical study sites, laboratories, consultants or other clinical trial vendors that perform the activities. The Company recognizes the reimbursement associated with collaborative activities to its collaborative partners as research and development expense in the period the services are provided.

### ***Leases***

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

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company does not have financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. Prospectively, the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company’s assessment unless there is reasonable certainty that the Company will renew.

Assumptions made by the Company at the commencement date are re-evaluated upon occurrence of certain events, including a lease modification. A lease modification results in a separate contract when the modification grants the lessee an additional right of use not included in the original lease and when lease payments increase commensurate with the standalone price for the additional right of use. When a lease modification results in a separate contract, it is accounted for in the same manner as a new lease.

### ***Equity Based Compensation Expense***

The Company’s share-based compensation programs grant awards that have included stock options, restricted stock units and restricted stock awards. Grants are awarded to employees and non-employees, including directors.

The Company accounts for its stock-based compensation awards in accordance with ASC Topic 718, Compensation—Stock Compensation (“ASC 718”). ASC 718 requires all stock-based payments to employees and non-employee directors, including grants of employee stock options and restricted stock units and modifications to existing stock options, to be recognized in the consolidated statements of operations and comprehensive income (loss) based on their fair values. The Company uses the Black-Scholes option pricing model to determine the fair value of options granted.

The Company accounts for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Stock-based compensation expense recognized in the financial statements is based on awards for which performance or service conditions are expected to be satisfied.

Prior to the adoption of ASU No. 2018-07, *Compensation - Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”) on July 1, 2018, the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based compensation during the vesting terms for changes in the fair value of the awards. After adoption of ASU 2018-07, the measurement date for non-employee awards is the date of grant without changes in the fair value of the award.

The Company’s stock-based awards are subject to service or performance-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term. Compensation expense related to awards to employees and non-employees with performance-based vesting conditions is recognized based on the grant date fair value over the requisite service period using the accelerated attribution method to the extent achievement of the performance condition is probable.

The Company expenses restricted stock unit awards to employees based on the fair value of the award on a straight-line basis over the associated service period of the award.

The Company estimates the fair value of its option awards to employees, directors and non-employees using the Black-Scholes option pricing model, which requires the input of subjective assumptions, including (i) the expected stock price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. Due to the lack of complete company-specific historical and implied volatility data for the full expected term of the stock-based awards, the Company bases its estimate of expected volatility on a representative group of publicly traded companies in addition to its own volatility data. For these analyses, the Company selected companies with comparable characteristics to its own, including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected life of the stock-based awards. The Company computes historical volatility data using the daily closing prices for the selected companies’ shares during the equivalent period of the calculated expected term of the stock-based awards. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The Company has estimated the expected term of its employee stock options using the “simplified” method, whereby the expected term equals the arithmetic average of the vesting term and the original contractual term of the option, due to its lack of sufficient historical data. The risk-free interest rates for periods within the expected term of the option are based on the U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The Company has never paid, and does not expect to pay, dividends in the foreseeable future.

### ***Patent Costs***

Costs to secure and prosecute patent applications 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 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, 2019, and 2018, 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 12 for further details.

### ***Comprehensive Income (Loss)***

Comprehensive income (loss) consists of net income or loss and other comprehensive income (loss). Other comprehensive income (loss) consists of foreign currency translation adjustments.

### ***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 variable interest entity (“VIE”) in accordance with 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 ASC Topic 805, *Business Combinations* (“ASC 805”) at the date the reporting entity first becomes the primary beneficiary.

In February 2016, Casebia, was formed in the United Kingdom. In March 2016, upon consummation of the joint venture (“JV”), Bayer Healthcare LLC and certain of its affiliates (“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 has not historically consolidated Casebia’s results into the consolidated financial statements.

As described in Note 7, on December 13, 2019, Casebia became a fully-owned subsidiary and, as a result, the Company consolidated Casebia’s financial results accordingly from that point forward.

### ***Net Income (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 restricted stock units using the treasury stock method. See Note 10 for further details.

### ***New Accounting Pronouncements – Recently Adopted***

#### ***Leases***

As discussed above, the Company adopted ASC 842, using the required modified retrospective approach, effective January 1, 2019. The Company chose to apply the transition provisions as of the period of adoption. The Company elected the package of practical expedients permitted under the transition guidance within the new standard, which, among other things, allowed the Company to carry forward the historical lease classification. In addition, the Company elected the practical expedient not to apply the recognition requirements in the lease standard to short-term leases (a lease that at commencement date has a lease term of 12 months or less and does not contain a purchase option that it is reasonably certain to exercise) and the practical expedient that permits lessees to make an accounting policy election (by class of underlying asset) to account for each separate lease component of a contract and its associated non-lease components as a single lease component. The adoption of the new standard resulted in the recording net lease assets and lease liabilities of \$26.1 million and \$37.6 million, respectively, as of January 1, 2019. The difference between the additional lease assets and lease liabilities is primarily due to the change in classification of lease incentives from liabilities to a reduction in our net lease assets. The standard had no impact on our net loss or cash flows.

Impact of Adopting ASC 842 on the Financial Statements

	January 1, 2019 <i>Prior to ASC 842 Adoption</i>	ASC 842 Adjustment	January 1, 2019 <i>As Adjusted</i>
<b>Consolidated Balance Sheet Data (in thousands):</b>			
Prepaid expenses and other current assets <sup>(1)</sup>	\$ 9,658	\$ (553)	\$ 9,105
Operating lease assets <sup>(2)</sup>	\$ —	\$ 26,087	\$ 26,087
Deferred rent <sup>(3)(4)</sup>	\$ 1,026	\$ (1,026)	\$ —
Deferred rent non-current <sup>(3)</sup>	\$ 11,052	\$ (11,052)	\$ —
Operating lease liabilities <sup>(5)</sup>	\$ —	\$ 4,930	\$ 4,930
Non-current operating lease liabilities <sup>(5)</sup>	\$ —	\$ 32,682	\$ 32,682

(1) Represents reclassification of prepaid rent to operating lease assets.

(2) Represents capitalization of operating lease assets and reclassification of equipment licenses from prepaid expenses to operating lease assets, offset by reclassification of deferred rent to operating lease assets.

(3) Represents reclassification of deferred rent and tenant incentives to operating lease assets.

(4) As of December 31, 2018, the deferred rent balance was \$1,202, which included \$176 of sublease income received prior to year-end but not due until January 1, 2019.

(5) Represents recognition of operating lease liabilities.

***New Accounting Pronouncements – Not Yet Adopted***

***Credit Losses***

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments – Credit Losses (Topic 362): Measurement of Credit Losses on Financial Statements*. The new standard requires that expected credit losses relating to financial assets measured on an amortized cost basis and available-for-sale debt securities be recorded through an allowance for credit losses. It also limits the amount of credit losses to be recognized for available-for-sale debt securities to the amount by which carrying value exceeds fair value and also requires the reversal of previously recognized credit losses if fair value increases. The targeted transition relief standard allows filers an option to irrevocably elect the fair value option of ASC 825-10, *Financial Instruments-Overall*, applied on an instrument-by-instrument basis for eligible instruments. The new standard will be effective beginning January 1, 2020. The adoption of ASU 2016-13 is not expected to have a material impact on the Company's financial position or results of operations upon adoption.

**3. Property and Equipment, net**

Property and equipment, net, consists of the following (in thousands):

	As of December 31,	
	2019	2018
Computer equipment	\$ 727	\$ 443
Furniture, fixtures, and other	3,215	2,453
Laboratory equipment	16,640	8,964
Leasehold improvements	21,400	13,776
Construction work in process	1,394	239
Total property and equipment, gross	43,376	25,875
Accumulated Depreciation	(12,046)	(7,375)
Total property and equipment, net	<u>\$ 31,330</u>	<u>\$ 18,500</u>

Depreciation expense for the year ended December 31, 2019, 2018, and 2017 was \$4.7 million, \$3.5 million, and \$3.0 million, respectively.

#### 4. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31,	
	2019	2018
Payroll and employee-related costs	\$ 15,229	\$ 7,321
Research costs	9,434	7,973
Licensing fees	750	625
Professional fees	2,040	1,848
Intellectual property costs	2,311	2,193
Accrued property and equipment	407	294
Other	9	598
Total	<u>\$ 30,180</u>	<u>\$ 20,852</u>

#### 5. Leases

In June 2015, the Company entered into a lease agreement for the lease of research facility space in Cambridge, Massachusetts, with a commencement date of November 15, 2015 (the “2015 Lease”). The lease expires in February 2022 with no further option to extend. The 2015 Lease contains escalating rent clauses, which require higher rent payments in future years. With the adoption of ASC 842, the Company has recorded a right-of-use asset and corresponding lease liability.

In May 2016, the Company entered into a sublease agreement for its primary office and research facility in Cambridge, Massachusetts, with a commencement date of December 23, 2016 (the “2016 Sublease”). The sublease expires in December 2026, and the Company has an option to extend the term of the sublease for an additional five-year period if, at the time of expiration of the initial term, the sublessor does not intend to utilize the space for itself or its affiliates. The 2016 Sublease contains escalating rent clauses, which require higher rent payments in future years. With the adoption of ASC 842, the Company has recorded a right-of-use asset and corresponding lease liability. The right-of-use asset and corresponding lease liability does not include the additional five-year period under the renewal option as the Company is not reasonably certain not to exercise that option.

In May 2019, the Company entered into a lease agreement for office facility space in Cambridge, Massachusetts, with a commencement date of June 1, 2019 (the “2019 Lease”). The lease expires in November 2026, and the Company has an option to extend the term of the lease for an additional five-year period based on certain conditions within the Company’s control. The 2019 Lease contains escalating rent clauses which require higher rent payments in future years. At lease commencement, the Company recorded a right-of-use asset and corresponding lease liability. The right-of-use asset and corresponding lease liability does not include the additional five-year period under the renewal option as the Company is not reasonably certain not to exercise that option.

In December 2019, Casebia became a wholly-owned subsidiary of the Company. In connection therewith, Casebia assigned its sublease for an office and research facility in Cambridge, Massachusetts (“2019 Sublease”) to the Company. The sublease expires in March 2024 and the Company has an option to extend the term of the sublease for an additional five-year period if, at the time of expiration of the initial term, the sublessor does not intend to utilize the space for itself or its affiliates. The 2019 Sublease contains escalating rent clauses which require higher rent payments in future years. The Company recorded a right-of-use asset and corresponding lease liability. The right-of-use asset and corresponding lease liability does not include the additional five-year period under the renewal option as the Company is not reasonably certain not to exercise that option.

In addition, the Company rents certain office space in Zug, Switzerland, on a short-term basis for which a right-of-use asset and liability are not recorded, in accordance with the practical expedient elected.

The Company has embedded leases in certain research and license agreements for which the Company has recorded a right of use asset and liability. These arrangements are not significant in comparison to the Company’s total operating lease assets and liabilities. In addition, the Company has identified certain short-term leases embedded within its manufacturing contracts which are not recorded on the Company’s balance sheet in accordance with the practical expedient elected.

The Company identified and assessed the following estimates in recognizing the right-of-use asset and corresponding liability:

- *Expected lease term:* The expected lease term for those leases commencing prior to January 1, 2019 did not change with the adoption of ASC 842. The expected lease term for leases commencing after the adoption of ASC 842 includes noncancelable lease periods and, when applicable, periods covered by an option to extend the lease if the Company is reasonably certain to exercise that option, as well as periods covered by an option to terminate the lease if the Company is reasonably certain not to exercise that option.
- *Incremental borrowing rate:* As the discount rates in the Company's lease are not implicit, the Company estimated the incremental borrowing rate based on the rate of interest the Company would have to pay to borrow a similar amount on a collateralized basis over a similar term.

The following table summarizes the lease assets and liabilities as of December 31, 2019 (in thousands):

	As of December 31, 2019	
<b>Assets</b>		
Operating lease assets	\$	41,502
Total lease assets		41,502
<b>Liabilities</b>		
Current		
Operating lease liabilities		8,489
Non-current		
Operating lease liabilities, net of current portion		44,050
Total lease liabilities	\$	<u>52,539</u>

The following table summarizes operating lease costs included in research and development and general and administrative expense, as well as sublease income for the twelve months ended December 31, 2019 (in thousands):

	Twelve Months Ended December 31, 2019	
Operating lease costs	\$	8,067
Short-term lease costs		4,554
Variable lease costs		4,282
Sublease income		(525)
<b>Net lease cost</b>	<b>\$</b>	<b><u>16,378</u></b>

The following table summarizes the maturity of undiscounted payments due under lease liabilities and the present value of those liabilities as of December 31, 2019 (in thousands):

	Total	
2020	\$	13,963
2021		11,824
2022		10,167
2023		10,269
2024		8,308
Thereafter		15,678
Total	\$	70,209
Present value adjustment		(17,670)
Present value of lease liabilities	\$	<u>52,539</u>



The following table summarizes the lease term and discount rate as of December 31, 2019:

	As of December 31, 2019
Weighted-average remaining lease term (years)	
Operating leases	6.0
Weighted-average discount rate	
Operating leases	9.9%

The following table summarizes the cash paid for amounts included in the measurement of lease liabilities for the twelve months ended December 31, 2019 (in thousands):

	Twelve Months Ended December 31, 2019	
Cash paid for amounts included in the measurement of lease liabilities	\$	8,420
Operating cash flows from operating leases	\$	<u>8,420</u>

In November 2019, the Company, together with one of its partners, committed to making payments to a clinical manufacturing organization under a lease arrangement. The lease arrangement is expected to commence in the second half of 2020, at which time an upfront payment of \$2.6 million is due. In addition, the Company and its partner have committed to paying approximately \$3.7 million in annual rental payments for a five-year period following commencement. All payments will be split equally between the Company and its partner.

## 6. Commitments and Contingencies

### *Intellectual Property Agreements*

#### *Patent Assignment Agreement*

In November 2014, the Company entered into a 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. As a result, the Assignors are entitled to receive certain low single digit clinical milestone payments and low single digit royalties based on annual net sales of licensed products and licensed services by the Company, its affiliates and sublicensees.

#### *Charpentier License Agreements*

In April 2014, the Company entered into certain technology license agreements with Dr. 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. In connection therewith, Dr. Charpentier is entitled to receive nominal clinical milestone payments, low single digit percentage of sublicensing payments received under any sublicense agreement with a third party, and low single-digit percentage royalties based on annual net sales of licensed products and services by the Company and its affiliates and sublicensees.

During the years ended December 31, 2019, 2018 and 2017, the Company paid an immaterial amount of fees to Dr. Charpentier, which were recorded as research and development expense.

### *Research, Manufacturing and License Agreements*

The Company has engaged several research institutions and companies to identify new delivery strategies and applications of the gene-editing technology. The Company is also a party to a number of research license agreements which require significant upfront payments, and may require future royalty payments and potential milestone payments from time to time. In addition, the Company is also a party to intellectual property agreements, which require maintenance and milestone payments from time to time. Further, the Company is a party to a number of manufacturing agreements that require upfront payments for the future performance of services.

In association with these agreements, on a product by product basis, the counterparties are eligible to receive up to low eight-digit potential payments upon specified research, development and regulatory milestones. In addition, on a product by product basis, the counterparties are eligible to receive potential commercial milestone payments based on specified annual sales thresholds. The potential payments are low-single digit percentages of the specified annual sales thresholds. The counterparties are also eligible to receive low single-digit royalties on future net sales.

Under certain circumstances and if certain contingent future events occur, Vertex is eligible to receive up to \$395.0 million in potential specified research, development, regulatory and commercial milestones and tiered single-digit royalties on future net sales. Refer to Note 7 for further discussion on the Company's arrangements with Vertex.

### ***Litigation***

The Company licenses a U.S. patent application from Dr. Charpentier that was subject to interference proceedings declared by the Patent Trial and Appeal Board ("PTAB") of the U.S. Patent and Trademark Office ("USPTO"). 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 June 2019, we received notification that the USPTO initiated a new interference proceeding at the PTAB, which the PTAB redeclared in August 2019. The '115 interference involves fourteen (14) pending U.S. patent applications co-owned by the CVC Group and thirteen (13) patents and a patent application owned by the Broad. Specifically, the PTAB declared the '115 interference between the CVC Group's pending U.S. Patent Application Nos. 15/947,680; 15/947,700; 15/947,718; 15/981,807; 15/981,808; 15/981,809; 16/136,159; 16/136,165; 16/136,168; 16/136,175; 16/276,361; 16/276,365; 16/276,368; and 16/276,374, and the Broad's U.S. Patent Nos. 8,697,359; 8,771,945; 8,795,965; 8,865,406; 8,871,445; 8,889,356; 8,895,308; 8,906,616; 8,932,814; 8,945,839; 8,993,233; 8,999,641; 9,840,713, and U.S. Patent Application No. 14/704,551. This list includes the same twelve Broad patents and application that were involved in the '048 interference. In contrast, none of the issued U.S. patents the CVC Group owns are subject to this proceeding. The CVC Group's inventions that are the subject of the '115 interference were first filed with the USPTO in May of 2012, while the Broad filed its first application seven months later in December of 2012. However, the 14 CVC Group patent applications that are involved in the '115 interference are continuing patent applications that were filed in 2018 and claim priority to the CVC Group's original 2012 filing, while the Broad's involved patents and patent application were filed between 2013 and 2015. Because the PTAB accorded neither party the benefit of any of its first filing dates, but instead accorded only the benefit of the actual filing dates of the involved patents and patent applications, the CVC Group was by default named the Junior Party. Both parties have filed motions requesting the benefit of their earliest priority dates (CVC in May of 2012 and the Broad in December of 2012) during 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 Regents of the University of California, University of Vienna, Dr. Charpentier, Intellia Therapeutics, Inc. Caribou Biosciences, Inc., ERS Genomics Ltd. and one of our subsidiaries. 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, 2019, 2018 and 2017, the Company incurred \$2.9 million, \$2.4 million and \$1.2 million, respectively, in shared costs. The Company recorded accrued legal costs from the cost sharing of \$1.5 million and \$1.9 million as of December 31, 2019 and December 31, 2018, respectively. 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.

In addition to the above, in the ordinary course of business, the Company is from time to time involved in lawsuits, claims, investigations, proceedings, and threats of litigation relating to intellectual property, commercial arrangements, employment and other matters. While the outcome of those proceedings and claims cannot be predicted with certainty, the Company is not party to any legal or arbitration proceedings that may have significant effects on its financial position. It is not a party to any material proceedings in which any director, member of executive management or affiliate of the Company is either a party adverse to it or its subsidiaries or has a material interest adverse to it or its subsidiaries.

## 7. Significant Contracts

### *Agreements with Vertex Pharmaceuticals Incorporated and certain of its subsidiaries*

#### *Summary*

On October 26, 2015, the Company entered into a strategic collaboration, option and license agreement (the “2015 Collaboration Agreement”) with Vertex Pharmaceuticals Incorporated and certain of its subsidiaries (“Vertex”). The 2015 Collaboration Agreement is focused on the use of the Company’s CRISPR/Cas9 gene-editing technology 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 2015 Collaboration Agreement (“Amendment No. 1”) and the Joint Development Agreement (the “JDA”). Amendment No. 1, among other things, modified certain definitions and provisions of the 2015 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 2015 Collaboration Agreement. Amendment No. 1 also amended other provisions of the 2015 Collaboration Agreement, including the expiration terms.

In connection with the 2015 Collaboration Agreement, Vertex made a nonrefundable upfront payment of \$75.0 million. Under the 2015 Collaboration Agreement, Vertex agreed to fund 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 No. 1, 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. In connection with the JDA, the Company received a \$7.0 million up-front payment from Vertex and subsequently received a one-time low seven-digit milestone payment upon the dosing of the second patient in a clinical trial with the initial product candidate. In addition, upon execution of the JDA and Amendment No. 1, it was clarified that Vertex may elect to license up to four remaining targets, for which it will lead global development and commercialization activities and the Company received the right to receive up to \$420.0 million in development, regulatory and commercial milestones and royalties on net product sales for each of the targets (inclusive of \$10 million due upon exercise of each exclusive option).

In June 2019, the Company and Vertex entered into a series of agreements, which closed on July 23, 2019, including a strategic collaboration and license agreement (the “2019 Collaboration Agreement”) for the development and commercialization of products for the treatment of Duchenne Muscular Dystrophy (“DMD”) and Myotonic Dystrophy Type 1 (“DM1”). Under the terms of the 2019 Collaboration Agreement, the Company received an upfront, nonrefundable payment of \$175.0 million. In addition, the Company is eligible to receive potential future payments of up to \$825.0 million based upon the successful achievement of specified research, development, regulatory and commercial milestones for the DMD and DM1 programs. The Company is also eligible to receive tiered royalties on future net sales on any products that may result from this collaboration. For the DMD program, Vertex is responsible for all research, development, manufacturing and commercialization activities and all related costs. For the DM1 program, the Company will perform specified guide RNA research and Vertex is responsible for all other research, development, manufacturing and commercialization costs. Upon Investigational New Drug (“IND”) application filing, the Company has the option to forego the DM1 milestones and royalties and instead, co-develop and co-commercialize all DM1 products globally in exchange for payment of 50% of research and development costs incurred by Vertex from the effective date of the agreement through IND filing.

In connection with the execution of the 2019 Collaboration Agreement, the Company and Vertex entered into a second amendment to the 2015 Collaboration Agreement (“Amendment No. 2”). Among other things, Amendment No. 2 modified certain definitions and provisions of the 2015 Collaboration Agreement to make them consistent with the 2019 Collaboration Agreement and set forth the number and identity of the collaboration targets under the 2015 Collaboration Agreement. The Company and Vertex agreed that one of the four remaining options under the 2015 Collaboration Agreement, as amended, would not be exercised; instead, the Company will reacquire the exclusive rights and will conduct research and development activities for the specified target. Vertex will have the option to co-develop and co-commercialize the specified target upon IND filing in exchange for payment of 50% of research and development costs incurred by the Company from the effective date of the agreement through IND filing. If Vertex does not exercise its option to co-develop and co-commercialize the specified target, Vertex is eligible to receive up to \$395.0 million in potential specified research, development, regulatory and commercial milestones and tiered single-digit royalties on future net sales.

In October 2019, Vertex exercised the remaining three options granted to it under the 2015 Collaboration Agreement to exclusively license the collaboration targets developed under the 2015 Collaboration Agreement, resulting in a payment of \$30.0 million to the Company in the fourth quarter of 2019.

#### *Accounting for the Vertex Agreements*

The 2015 Collaboration Agreement, Amendment No. 1, and JDA are collectively the “2015 Agreements” and the 2019 Collaboration Agreement and Amendment No. 2. are collectively the “2019 Agreements.” The 2015 Collaboration Agreement, Amendment No. 1, Amendment No. 2, JDA and 2019 Collaboration Agreement are collectively the “Vertex Agreements.”

The Vertex Agreements include components of a customer-vendor relationship as defined under ASC 606, , collaborative arrangements as defined under ASC 808 and research and development costs as defined under ASC 730, *Research and Development* (“ASC 730”).

#### *Accounting Analysis Under ASC 606*

##### *Accounting for the 2019 Agreements*

##### *Identification of the Contract*

The 2019 Agreements represented a contract modification to the 2015 Agreements. As a result, the 2019 Agreements and the 2015 Agreements are combined for accounting purposes and treated as a single arrangement.

##### *Identification of Performance Obligations*

The Company concluded the following material promises were both capable of being distinct and distinct within the context of the Vertex Agreements and represented separate performance obligations: (i) an exclusive license for worldwide rights for DMD gene editing products (“DMD License”); (ii) an exclusive license for worldwide rights for DM1 gene editing products (“DM1 License”); (iii) the performance of specified guide RNA research for DM1 (“DM1 R&D Services”); (iv) a material right representing the option to obtain a co-exclusive development and commercialization license for a specified target (“Specified Target Option”); (v) three material rights representing the option for up to three exclusive licenses to develop and commercialize the collaboration targets (“Collaboration Target Options”), and (vi) the waiving of Vertex’s material right associated with its option to a fourth exclusive license in connection with the Company’s reacquisition of exclusive rights to the specified target.

##### *Determination of Transaction Price*

The overall transaction price was determined based on the remaining transaction price from the 2015 Agreements, as well as the transaction price from the 2019 Agreements. The transaction price includes variable consideration estimated using the most likely amount methodology. As such, the Company determined the transaction price totaling \$268.6 million was comprised of: (i) \$57.8 million of pre-existing deferred revenue from the 2015 Agreements; (ii) non-cash consideration of \$10.0 million related to the waiving of Vertex’s material right associated with its option to a fourth exclusive license in connection with the Company’s reacquisition of exclusive rights to the specified target; (iii) an upfront payment of \$175.0 million; (iv) variable consideration of \$25.0 million which represents the Company’s estimate related to a near-term research and development milestone for which the Company determined that it is not probable that a significant reversal of cumulative consideration will occur; and (v) variable consideration of \$0.8 million which represents the Company’s estimate of payments from Vertex for DM1 R&D Services.

The Company determined that all other possible variable consideration resulting from milestones and royalties discussed above was fully constrained as of December 31, 2019. The Company will re-evaluate the transaction price in each reporting period.

##### *Allocation of Transaction Price to Performance Obligations*

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 Vertex Agreements 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 then allocated the transaction price to each performance obligation on a relative standalone selling price basis.

The ESSP for the DMD License and DM1 License was determined to be \$224.6 million and \$76.2 million, respectively. The ESSP was determined based on probability and present value adjusted cash flows from projected worldwide net profit for each of the respective programs based on probability assessments, projections based on internal forecasts, industry data, and information from other guideline companies within the same industry and other relevant factors. On a relative basis \$151.1 million and \$51.3 million of the transaction price was allocated to the DMD License and DM1 License, respectively.

The ESSP for the Specified Target Option material right was determined to be \$17.5 million, which was based on the incremental discount between (i) the value of the probability and present value adjusted cash flows from the equal sharing of projected worldwide net profit increased by the value of the option provided to Vertex less (ii) the expected exercise price at the time of option exercise. The present value adjusted cash flows also considered projections based on internal forecasts, industry data, and information from other guideline companies within the same industry and other relevant factors. On a relative basis \$11.8 million of the transaction price was allocated to the Specified Target Option material right.

The ESSP for each of the three Collaboration Target Option material rights was determined to be \$25.0 million, \$22.2 million and \$22.2 million, respectively, which was determined based the probability and present value adjusted cash flows from milestone payments owed for exclusive licenses, less the price paid to exercise each option. On a relative basis \$46.7 million of the transaction price was allocated to the Collaboration Target Option material rights.

The aforementioned ESSPs reflect the level of risk and expected probability of success inherent in the nature associated of the associated research area.

The ESSP for the waiving of Vertex's material right associated with its option to a fourth exclusive license under the 2015 Agreements was determined to be \$10.0 million, or the contractual value of the option. On a relative basis \$6.7 million of the transaction price was allocated to the waiving of Vertex's material right associated with its option to a fourth exclusive license under the 2015 Agreements.

The ESSP for the DM1 R&D Services was determined to be \$1.7 million, which was based on 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. On a relative basis \$1.1 million of the transaction price was allocated to the DM1 R&D Services.

#### *Recognition of Revenue*

The Company determined that the DMD License and DM1 License represent functional intellectual property, as the intellectual property provides Vertex with the ability to perform a function or task in the form of research and development. As such, the revenue related to the licenses was recognized at the point in time in which they were delivered during the third quarter of 2019.

The revenue allocated to the waiving of Vertex's material right associated with its option to a fourth exclusive license in connection with Company's reacquisition of exclusive rights to the specified target was recognized at the point in time in which the option was waived, on the effective date of the 2019 Agreements.

The Company concluded that the Specified Target Option and Collaboration Target Options are considered material rights under the Vertex Agreements. Revenue related to the three Collaboration Target Options material right was recognized at the point in time in which Vertex exercised the Collaboration Target Options, which occurred in the fourth quarter of 2019. In addition, the Company recognized \$30.0 million in revenue corresponding to the three \$10.0 million payments made by Vertex to exercise the three options, the consideration for which, the Company determined relates specifically to the Company's efforts to satisfy the respective performance obligations (material rights) and that allocating the amounts to those performance obligations (material rights) satisfies allocation objectives in ASC 606-10-32-28.

The Company recognizes revenue related to the DM1 R&D Services over time as the services are rendered, which is expected to be over an 18-month period from the effective date of the 2019 Agreements.

#### *Accounting for the 2015 Agreements (prior to the execution of the 2019 Agreements)*

On January 1, 2018, the Company adopted ASC 606 using the modified retrospective approach. 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. There was no significant impact on revenue recognized under ASC 606 and the prior revenue recognition as a result of the adoption.

#### *Identification of the Contract*

Amendment No. 1 and the JDA represented a contract modification to the 2015 Collaboration Agreement. As a result, the 2015 Agreements are combined for accounting purposes and treated as a single arrangement.

### *Identification of Performance Obligations*

The Company concluded the following material promises were both capable of being distinct and distinct within the context of the 2015 Agreements and represented separate 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.

### *Determination of Transaction Price*

The overall transaction price was 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 Company determined that all other possible variable consideration resulting from milestones and royalties discussed above was fully constrained as of December 31, 2018 and 2017. The Company will re-evaluate the transaction price in each reporting period.

### *Allocation of Transaction Price to Performance Obligations*

The selling price of each performance obligation was determined based on the Company's ESSP. The Company developed the ESSP for all the performance obligations included in the 2015 Agreements 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 then allocated the transaction price to each performance obligation on a relative standalone selling price basis.

The ESSP for R&D Services was determined to be \$19.3 million. 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 allocated \$19.3 million of the transaction price to R&D Services.

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 the probability and present value adjusted cash flows from milestone payments owed for exclusive licenses, less the price paid to exercise each option. On a relative basis \$57.7 million of the transaction price was allocated to these material rights.

The Company's ESSP for the co-exclusive research license and the development and commercialization licenses for hemoglobinopathy and beta-globin targets is \$48.9 million. The ESSP for this item was determined based on probability and present value adjusted cash flows from the equal sharing of projected worldwide net profit. ESSP reflects the level of risk and expected probability of success inherent in the nature of the associated research area. On a relative basis \$23.8 million of the transaction price was allocated to the co-exclusive research license and the development and commercialization licenses for hemoglobinopathy and beta-globin targets.

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. On a relative basis \$0.5 million of the transaction price was allocated to the non-exclusive research license.

The aforementioned ESSP's reflect the level of risk and expected probability of success inherent in the nature of the associated research area.

### *Recognition of Revenue*

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 was 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. 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, the Company recognized revenue related to the R&D services as invoiced, in line with the practical expedient in ASC 606-10-55-18.

### *Revenue recognized in connection with the Vertex Agreements*

During the years ended December 31, 2019, 2018 and 2017, the Company recognized \$289.1 million, \$0.6 million and \$36.2 million of revenue related to the Vertex Agreements, respectively. The \$289.1 million of revenue recognized for the year-ended December 31, 2019 was comprised of (i) revenue related to the DMD License and DM1 License of \$202.4 million, which was recognized at the point in time in which the licenses were delivered, (ii) revenue related to the Collaboration Target Options by Vertex, (iii) revenue allocated to the waiving of Vertex's material right associated with its option to a fourth exclusive license in connection with the Company's reacquisition of exclusive rights to the specified target of \$6.7 million, which was recognized at the point in time in which the option was waived, (iv) revenue recognized in connection with DM1 R&D Services of \$0.1 million and (v) revenue recognized of \$0.1 million related to both research and development services as well as the amortization of the non-exclusive research license under the 2015 Agreements. Additionally, the Company recognized revenue related to a one-time low seven-digit milestone payment upon the dosing of the second patient in a clinical trial with the initial product candidate in the third quarter of 2019. The \$0.6 million in revenue recognized in 2018 was comprised of both research and development services as well as the amortization of the non-exclusive research license under the 2015 Agreements. The \$36.2 million of revenue recognized in 2017 was comprised of primarily of (i) \$30.3 million allocated to co-exclusive research license and a development and commercialization license to develop and commercialize each of the hemoglobinopathy and beta-globin targets under ASC 605, which was recognized in connection with the signing of the JDA in December 2017 and (ii) research and development services under the 2015 Agreements.

As of December 31, 2019 and 2018, there was \$0.9 million and \$0.1 million of current deferred revenue related to the Vertex Agreements. As of December 31, 2019 and 2018, there was \$11.8 million and \$57.8 million of non-current deferred revenue related to the Vertex Agreements. The transaction price allocated to the remaining performance obligations was \$12.7 million.

### *Milestones under the Vertex Agreements*

The Company has evaluated the milestones that may be received in connection with the Vertex Agreements. As discussed above, in connection with the Collaboration Target Options, the Company received \$30.0 million in option exercise payments from Vertex in the fourth quarter of 2019. The Company is eligible to receive up to \$410.0 million in additional development, regulatory and commercial milestones and royalties on net product sales for each of the three collaboration targets that Vertex licensed in the fourth quarter of 2019. 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.

In connection with the JDA, the Company received a one-time low seven-digit milestone payment upon the dosing of the second patient in a clinical trial with the initial product candidate. Revenue was recognized for this milestone in the third quarter of 2019, the point in time in which the milestone was both probable and achieved.

The Company is eligible to receive potential future payments of up to \$825.0 million based upon the successful achievement of specified research, development, regulatory and commercial milestones for the DMD and DM1 programs. As discussed above, the first research milestone of \$25.0 million was included in the transaction price. This amount is recorded as a contract asset within prepaid expenses and other current assets on the condensed consolidated balance sheet. The Company is also eligible to receive tiered royalties on future net sales on any products that may result from this collaboration; however, the Company has the option to forego the DM1 milestones and royalties to co-develop and co-commercialize all DM1 products globally.

With the exception of the first research milestone of \$25.0 million, each of the remaining milestones are fully constrained as of December 31, 2019. There is uncertainty that the events to obtain the research and developmental milestones will be achieved given the nature of clinical development and the stage of the CRISPR/Cas9 technology. The remaining research, development and regulatory milestones will be constrained until it is probable 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 are accounted for under the royalty recognition constraint and will be accounted for as constrained variable consideration. The Company applies 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.

### *Accounting Analysis under ASC 808*

In connection with the 2019 Agreements, the Company identified the following collaborative elements, which were unchanged as those identified with the 2015 Agreements and are accounted for under ASC 808: (i) development and commercialization services for shared products; (ii) R&D Services for follow-on products; and (iii) committee participation. The related impact of the cost sharing associated with research and development is included in research and development expense. Expenses related to services performed by the Company are classified as research and development expense. Payments received from Vertex for partial reimbursement of expenses are recorded as a reduction of research and development expense.

During the years ended December 31, 2019, 2018 and 2017, the Company recognized \$29.2 million, \$20.2 million and \$9.9 million of research and development expense related to the Vertex Agreements. Research and development expense for 2019, 2018 and 2017 is net of \$15.9 million, \$13.8 million and \$0.0 million of reimbursements from Vertex, respectively.

#### *Accounting Analysis under ASC 730*

In connection with the 2019 Vertex Agreements, the Company and Vertex agreed that one of the four remaining options under the 2015 Agreements, as amended, would not be exercised; instead, the Company will conduct research and development activities for a specified target. Vertex will have the option to co-develop and co-commercialize the specified target upon IND filing in exchange for payment of 50% of research and development costs incurred by the Company from the effective date of the agreement through IND filing. If Vertex does not exercise its option to do so within a specified time period, Vertex is eligible to receive up to \$395.0 million in potential specified research, development, regulatory and commercial milestones and tiered single-digit royalties on future net sales.

In connection therewith, the Company determined that in order for the Company to obtain the right to conduct research and development activities on the specified target, the Company had waived its right to receive an option exercise payment of \$10.0 million from Vertex, which was included as non-cash consideration in the transaction price described above. The Company then subsequently reacquired its rights to the specified target by waiving payment owed by Vertex of \$10.0 million for a license that represents in-process research and development and therefore, \$10.0 million of non-cash consideration was fully expensed upon the execution of the 2019 Agreements. The Company also determined that research and development services through IND for the specified target and any payment of future development and commercialization milestones, as well as sales-based milestones and royalties for the specified target, would be accounted for as research and development costs under ASC 730 and expensed as incurred. In addition, the Company also determined that should the Company elect its option to co-develop and co-commercialize all DM1 products globally, it will record the option fee as research and development expense upon exercise.

#### *Joint Venture with Bayer Healthcare LLC*

##### *Summary*

On December 19, 2015, the Company entered into an agreement with Bayer, to establish a joint venture to focus on the research and 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. Bayer and the Company each received a 50% equity interest in the entity in exchange for their respective contributions to the entity. At this time, the Company also entered into a separate service agreement with Casebia, under which the Company agreed to provide compensated research and development services. Collectively, these agreements are referred to as the “2015 Casebia Agreements.”

On December 13, 2019, the Company, Bayer and Casebia entered into a series of transactions by which, among other things, the Company acquired 100% of the partnership interests in Casebia (“Retirement Agreement”), the Company and Bayer terminated their joint venture (“Joint Venture Termination Agreement”), and the Company and Bayer entered into a new option agreement (the “2019 Option Agreement”). Collectively, these agreements are referred to as the “2019 Casebia Agreements.”

In connection with the Retirement Agreement, Casebia retired Bayer’s outstanding partnership interests in exchange for up to \$22.0 million returned from Casebia operating cash less certain estimated interim operating expenses of \$6.0 million, which is subject to potential post-closing adjustments, and the Company acquired 100% of the partnership interests in Casebia.

In connection with entering into the Retirement Agreement, the Company, Bayer and Casebia entered into the Joint Venture Termination Agreement. In connection therewith, the Company and Bayer agreed to terminate the Joint Venture Agreement from December 2015. Under the Joint Venture Termination Agreement, Casebia-owned patents will now be co-owned by the Company and Bayer, subject to certain exclusive licenses granted therein. Under the Joint Venture Termination Agreement, the Company and Bayer each retained rights to their respective contributed intellectual property.

In connection with entering into the Retirement Agreement and the Joint Venture Termination Agreement, the Company and Bayer also entered into the 2019 Option Agreement, under which, among other things, the Company committed to invest a specified amount in certain research and development activities as described under “Accounting Analysis – Accounting for 2019 Casebia Agreements”. In addition, Bayer has an option (exercisable during a specified exercise period defined by future events, but in no event longer than 5 years after the effective date of the 2019 Option Agreement) to co-develop and co-commercialize two products for the diagnosis, treatment or prevention of certain autoimmune disorders, eye disorders, or hemophilia A disorders. In the event Bayer elects to co-develop and co-commercialize a product, the parties will negotiate and enter into a co-development and co-commercialization agreement (a “Co-Commercialization Agreement”) for such product, and Bayer would be responsible for 50% of the research and development costs incurred by the Company for such product going forward. Bayer would receive 50% of all profits from sales of such product and would be responsible for 50% of all losses.



If Bayer elects to exercise its option to co-develop and co-commercialize a product, Bayer will make a one-time \$20.0 million payment (the “Option Payment”) to the Company that will become non-refundable once the parties execute a Co-Commercialization Agreement with respect to such optioned product. The Option Payment is payable only once with respect to the first time Bayer exercises an option under the 2019 Option Agreement.

In addition, following Bayer’s exercise of its option and/or the execution of a Co-Commercialization Agreement for an optioned product, for a period beginning on the effective date of such Co-Commercialization Agreement and ending on the earlier of the 3 month anniversary of such effective date or during the 90-day negotiation process of such Co-Commercialization Agreement, Bayer has a right to negotiate an exclusive license to develop and commercialize such optioned product. If Bayer exercises such right, the parties will enter into an exclusive license agreement for such optioned product on terms mutually agreeable to the parties. Further, the Option Payment paid for such optioned product would become credited against payments due under such exclusive license or any other exclusive license entered into in connection with the 2019 Option Agreement.

Either party may terminate the 2019 Option Agreement upon the other party’s material breach, subject to specified notice and cure provisions. The Company may also terminate the 2019 Option Agreement in the event Bayer commences or participates in any action or proceeding challenging the validity or enforceability of any Company patent necessary or useful for the research, development, manufacture or commercialization of a product that is the subject of the 2019 Option Agreement. Bayer may also terminate the 2019 Option Agreement upon the Company’s bankruptcy or insolvency, or for convenience at any time, after giving written notice.

### *Accounting Analysis*

#### *Accounting for the 2015 Casebia Agreements*

The Company determined that Casebia was a VIE and concluded that the Company was not the primary beneficiary of the VIE. As such, the Company did not consolidate Casebia’s results into the consolidated financial statements. Instead, the Company accounted for its ownership in Casebia as an equity method investment, the value of which was written down to zero immediately after formation of the joint venture. The 2015 Casebia Agreements included components of a customer-vendor relationship as defined under ASC 606 and collaborative arrangements as defined under ASC 808.

As discussed above, on January 1, 2018, the Company adopted ASC 606 using the modified retrospective approach. There was no significant impact on revenue recognized under ASC 606 and the prior revenue recognition as a result of the adoption.

For the years ended December 31, 2019, 2018 and 2017, the only element of 2015 Casebia Agreements accounted for in accordance with ASC 606 was the obligation to perform research and development services for Casebia. Revenue recognized for research and development was recognized under the right to invoice practical expedient in ASC 606-10-55-18. This performance obligation was terminated upon the execution of the 2019 Casebia Agreements.

For the years ended December 31, 2019, 2018 and 2017, the only element of the 2015 Casebia Agreements accounted for in accordance with ASC 808 was the cost sharing activity with Casebia with respect to shared research and technology licenses with other vendors for which the Company determined the arrangement was a cost/profit sharing arrangement and not a revenue arrangement. Therefore, the related impact of the cost sharing is included in R&D expense. Cost sharing activity ceased with the execution of the 2019 Casebia Agreements.

#### *Loss from Equity Method Investment*

During the years ended December 31, 2019, 2018 and 2017, the Company recognized \$5.5 million, \$4.3 million and \$1.8 million, respectively, of stock-based compensation expense related to Casebia employees. Unrecognized equity method losses in excess of the Company’s equity investment in Casebia was \$72.0 million and \$45.3 million as of December 31, 2019 and 2018, respectively. Total net loss of Casebia for the period ending December 31, 2019 (prior to the Company’s consolidation of Casebia) and the years ended December 31, 2018 and 2017 was \$58.8 million, \$52.5 million and \$36.2 million, respectively.

#### *Collaboration Revenue*

During the years ended December 31, 2019, 2018 and 2017, the Company recognized \$0.5 million, \$2.5 million and \$4.8 million of revenue, respectively, related to the collaboration with Casebia. During the years ended December 31, 2019, 2018 and 2017, the Company recognized \$0.7 million, \$3.8 million and \$4.5 million of research and development expense, respectively, in relation to its performance under the agreement.

### *Collaborative elements*

The Company received reimbursements of \$0.2 million, \$0.9 million and \$4.4 million for both research and license agreements during years ended December 31, 2019, 2018 and 2017, respectively, which was recorded as a reduction of R&D expense in the income statement.

### *Accounting for the 2019 Casebia Agreements*

The Company determined that the Retirement Agreement and Joint Venture Termination Agreement resulted in the Company obtaining a controlling interest in Casebia and should be accounted for as a separate component from the 2019 Option Agreement. In doing so, the Company allocated the consideration transferred of \$41.0 million (consisting of \$16.0 million of assets acquired net of the purchase price, as displayed in the table below, and \$25.0 million of cash allocated to the 2019 Option Agreement) between the two components using a relative fair value approach. The Company determined the relative fair value related to obtaining a controlling interest in Casebia was \$32.0 million and the relative fair value of the consideration transferred related to the 2019 Option Agreement was \$25.0 million, which is comprised of \$20.2 million related to certain research and development activities and \$4.8 million related to certain options as described above.

As a result of the Retirement Agreement, the Company determined that it had obtained a controlling interest in a VIE, for which it became the primary beneficiary. As such, under ASC 810, *Consolidation*, the Company accounted for the net assets obtained under ASC 805, *Business Combinations*. In accordance therewith, the Company determined the set of acquired assets and assumed liabilities did not meet the definition of a business, as the Company did not acquire an assembled workforce and thus the Company did not acquire substantive processes capable of producing outputs. As such, no goodwill was recorded. The Company measured the fair value of the assets and liabilities received, determining the relative fair value was \$16.0 million (after paying the \$16.0 million for Bayer's 50% interest) and recorded the difference between that amount and the Company's carrying amount, which was zero, as a gain within other income (expense). The relative fair value of the assets and liabilities received (exclusive of the \$16.0 million paid from Casebia to Bayer to retire Bayer's interest in the JV) was determined as follows (in thousands):

<b>Fair value</b>	<b>Amount</b>
Cash and cash equivalents	\$ 6,784
Prepaid expenses and other current assets	2,565
Property, plant and equipment, net	9,340
Operating lease assets	11,003
Restricted cash	1,226
Accrued expenses and other current liabilities	(3,915)
Operating lease liabilities	(11,003)
Net assets	<u>\$ 16,000</u>

The value of the reacquired rights related to the intellectual property was determined to be insignificant.

The Company determined that the 2019 Option Agreement should be accounted for under ASC 730-20, *Research and Development Expense*. This determination was based on the fact that the financial risk associated with the research and development has been transferred to the Company because repayment of any of the funds provided by Bayer depends solely on the results of the research and development having a future economic benefit. The Company further determined that it had two separate obligations under the 2019 Option Agreements, which consist of i) research and development services and ii) future delivery of up to two options for products in defined fields. The relative fair value of the obligations was determined to be \$20.2 million and \$4.8 million, respectively. As the Company has accounted for its obligations as a contract to perform research and development for others, with respect to the obligation to perform research and development services the Company will recognize an offset to research and development expense as the research is performed and, with respect to the future delivery of up to two option for products in defined fields, at the earlier of option exercise (at or near IND application filing), expiration, or when commercially reasonable efforts to progress the program have been exhausted.

The Company has recorded \$11.0 million in other current liabilities relating to certain research and development obligations to be satisfied within one year of the balance sheet date and \$14.0 million in other long-term liabilities consisting of the relative fair value of such obligations to be satisfied beyond one year from the balance sheet date as well as the relative fair value of the options. Further, the Company determined that Casebia was not significant in accordance with Regulation S-X Rule 3-05 and 3-09.

### ***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 for the twelve months ended December 31, 2018.

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. Under the agreement, each of the parties are obligated to use commercially reasonable efforts to perform certain research activities under a jointly developed research plan. Each party bears the costs for its respective research obligations.

## **8. Share Capital**

The Company had 103.9 million and 90.3 million authorized Common Shares as of December 31, 2019 and 2018, respectively, with a par value of CHF 0.03 per share. Share Capital consisted of the following (in thousands):

<b>Type of Share Capital</b>	<b>Conditional Capital</b>	<b>As of December 31,</b>	
		<b>2019</b>	<b>2018</b>
Common shares	Registered share capital	61,037	52,268
Common shares	Authorized share capital	19,246	17,577
Common shares	Conditional share capital - Bonds or similar debt instruments	4,920	4,920
Common shares	Conditional share capital - Employee benefit plans	18,698	15,579
	<b>Total</b>	<b>103,901</b>	<b>90,344</b>

Included in registered share capital are 1,230,729 shares registered, which are held by the Company and its subsidiaries and are reserved for future issuance for financings.

### ***Common Share Issuances***

In October 2016, the Company sold 4.4 million common shares through an initial public offering (inclusive of shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) at a price of \$14.00 per share for proceeds of \$53.7 million, which were net of equity issuance costs of \$8.3 million. Concurrent with the initial public offering, the Company sold 2.5 million common shares to Bayer BV in a private placement, at a price of \$14.00 per share, resulting in aggregate net proceeds of \$35.0 million.

In January 2018, the Company sold 5.7 million common shares through an underwritten public offering (inclusive of shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) at a price of \$22.75 per share for proceeds of \$122.6 million, which were net of equity issuance costs of \$8.2 million.

In September 2018, the Company sold 4.2 million common shares through an underwritten public offering at a price of \$47.50 per share for proceeds of \$184.5 million, which were net of equity issuance costs of \$15.5 million.

In the first quarter of 2019, the Company began to sell securities under an Open Market Sale Agreement<sup>SM</sup> it entered into with Jefferies LLC (“Jefferies”) in August 2018 (“2018 ATM”), under which the Company was able to offer and sell, from time to time, common shares having aggregate gross proceeds of up to \$125.0 million. During year ended December 31, 2019, the Company issued and sold an aggregate of 2.8 million common shares at an average price of \$44.38 per share for aggregate proceeds of \$120.6 million, which were net of equity issuance costs of \$4.4 million.

In November 2019, the Company sold 4.9 million common shares through an underwritten public offering (inclusive of shares sold pursuant to the exercise of the option to purchase additional shares granted to the underwriters in connection with the offering) at a price of \$64.50 per share for proceeds of \$294.4 million, which were net of equity issuance costs of \$20.7 million.

In addition, in August 2019, following the termination of the 2018 ATM by its terms, the Company entered into a new Open Market Sale Agreement<sup>SM</sup> with Jefferies (the “2019 ATM”), under which the Company may offer and sell, from time to time, common shares having aggregate gross proceeds of up to \$200.0 million. The Company has not yet issued or sold any securities under the 2019 ATM.

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.

### ***Dividends***

The holders of Common Shares are entitled to receive dividends, if and when resolved upon by the general meeting of shareholders based on a respective proposal by the Board of Directors and provided that the Company disposes of sufficient freely distributable reserves. As of December 31, 2019, 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.

## **9. Equity-based Compensation**

### ***Option and Grant Plans***

In April 2015, the Company’s shareholders approved the 2015 Stock Option and Grant Plan (the “2015 Plan”) and in July 2016, the Company’s shareholders approved the 2016 Stock Option and Incentive Plan (the “2016 Plan”). In May 2018, the Company’s shareholders approved the 2018 Stock Option and Incentive Plan (the “2018 Plan,” collectively, the “Plans”). Subsequent to the IPO, no further options were 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 Company’s Board of Directors, 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.

### ***Equity-Based Compensation Expense***

The Company recognized stock-based compensation expense totaling \$49.5 million, \$39.3 million, and \$20.6 million during the years ended December 31, 2019, 2018 and 2017, respectively. Stock-based compensation expense by classification within the consolidated statements of operations and comprehensive income (loss) is as follows (in thousands):

	Years Ended December 31,		
	2019	2018	2017
Research and development	\$ 23,273	\$ 17,557	\$ 8,800
General and administrative	20,784	17,428	10,073
Loss from equity method investment	5,467	4,275	1,763
Total	<u>\$ 49,524</u>	<u>\$ 39,260</u>	<u>\$ 20,636</u>

As of December 31, 2019, there was \$96.2 million and \$31.9 million of unrecognized compensation expense related to unvested stock options and restricted stock units, respectively, that is expected to be recognized over a weighted-average period of 2.8 and 2.3 years, respectively.

### *Stock Options*

The fair value of each option issued to employees and non-employees was estimated at the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	Years Ended December 31,		
	2019	2018	2017
Options granted	2,832,784	2,209,597	2,999,847
Weighted-average exercise price	\$ 39.16	\$ 51.73	\$ 16.98
Weighted-average grant date fair value	\$ 24.57	\$ 33.82	\$ 11.16
Assumptions:			
Expected volatility	68.9%	71.9%	72.5%
Expected term (in years)	6.0	6.0	6.1
Risk-free interest rate	2.2%	2.8%	2.0%
Expected dividend yield	0.0%	0.0%	0.0%

The following table summarizes stock option activity under the Company's equity award plans (intrinsic value in thousands):

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2018	6,689,311	\$ 25.42	8.3	\$ 68,572
Granted	2,832,784	\$ 39.16		
Exercised	(1,180,644)	\$ 14.91		
Cancelled or forfeited	(559,014)	\$ 35.35		
Outstanding at December 31, 2019	7,782,437	\$ 31.30	8.2	231,554
Exercisable at December 31, 2019	3,328,398	\$ 24.07	7.4	\$ 122,774
Vested and expected to vest at December 31, 2019	7,782,437	\$ 31.30	8.2	\$ 231,554

During 2019 and 2018, the Company did not grant awards subject to performance-based or market-based vesting conditions. As of December 31, 2019, options to purchase 883,695 Common Shares subject to performance-based vesting conditions were vested, as performance conditions were achieved, and there were 261,888 options to purchase Common Shares subject to performance-based vesting conditions outstanding.

During 2017, the Company granted 150,000 options with market-based vesting conditions, of which 75% vest at the end of a three-year service period and 25% vest at the end of a four-year service period. Upon achieving a specified average stock price in prior years, the market condition was satisfied. Expense for the options is being recognized over the requisite service period. As of December 31, 2019, none of the stock options had vested.

The total intrinsic value (the amount by which the fair market value exceeded the exercise price) of stock options exercised during the year ended December 31, 2019, 2018 and 2017 was \$42.2 million, \$38.3 million and \$12.3 million, respectively.

### *Restricted Stock*

The following table summarizes the restricted stock activity under the Company's equity award plans (shares in thousands):

	Shares	Weighted- Average Grant Date Fair Value
Unvested restricted common shares at December 31, 2018	327,342	\$ 36.72
Granted	503,600	62.11
Vested	(86,758)	20.38
Cancelled or forfeited	(44,650)	44.50
Unvested restricted common shares at December 31, 2019	<u>699,534</u>	<u>\$ 56.53</u>

During the years ended December 31, 2019, 2018 and 2017, the total fair value of restricted stock vested was \$3.6 million, \$11.3 million and \$8.3 million, respectively.

### *Award modifications*

During the years ended December 31, 2019, 2018 and 2017, the Company modified the terms of certain equity awards held by departing employees, resulting in \$0.1 million, \$3.8 million, and \$2.2 million of stock-based compensation expense, respectively. During the year ended December 31, 2019, the Company modified the terms of certain equity awards held by non-employees. The modifications resulted in \$2.9 million in stock-based compensation expense recorded during the period. For the year ended December 31, 2018 and 2017, there were no modification of options held by non-employees.

## 10. Net Income (Loss) Per Share Attributable to Common Shareholders

Basic net loss per share is calculated by dividing net 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 share equivalents 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 computation of basic and diluted net income (loss) per share for the periods ended (in thousands, except per share amounts):

	Year ended December 31,		
	2019	2018	2017
<i>Basic net income (loss) per common share calculation:</i>			
Net income (loss) attributable to common shareholders	\$ 66,858	\$ (164,981)	\$ (68,357)
Net income (loss) attributable to common shareholders - basic	\$ 66,858	\$ (164,981)	\$ (68,357)
Basic weighted-average common shares outstanding	54,392,304	47,964,368	40,057,365
Basic net income (loss) per common share	\$ 1.23	\$ (3.44)	\$ (1.71)
<i>Diluted net income (loss) per common share calculation:</i>			
Net income (loss) attributable to common shareholders	\$ 66,858	\$ (164,981)	\$ (68,357)
Net income (loss) attributable to common shareholders - diluted	\$ 66,858	\$ (164,981)	\$ (68,357)
Weighted-average shares used to compute basic net income (loss) per common share	54,392,304	47,964,368	40,057,365
Effect of potentially dilutive securities:			
Outstanding options	2,406,962	—	—
Unvested restricted common shares	133,532	—	—
Weighted-average shares used to compute diluted net income (loss) per common share	56,932,798	47,964,368	40,057,365
Diluted net income (loss) per common share	\$ 1.17	\$ (3.44)	\$ (1.71)

The Company did not include the securities in the following table in the computation of the net income (loss) per share calculations because the effect would have been anti-dilutive during each period:

	Year ended December 31,		
	2019	2018	2017
Outstanding options	3,789,129	6,689,311	6,262,339
Unvested restricted common shares	108,625	327,342	157,515
Total	<u>3,897,754</u>	<u>7,016,653</u>	<u>6,419,854</u>

## 11. 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 \$1.1 million, \$0.6 million and \$0.5 million to the 401(k) Plan for the year ended December 31, 2019, 2018 and 2017, respectively.

## 12. 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, 2019, 2018 and 2017, the income (loss) before provision for income taxes consist of the following (in thousands):

	Years Ended December 31,		
	2019	2018	2017
Domestic	\$ 9,155	\$ 5,966	\$ 5,184
Foreign	58,151	(170,394)	(71,792)
Total	\$ 67,306	\$ (164,428)	\$ (66,608)

The (provision for) benefit from income taxes consist of the following (in thousands):

	Years Ended December 31,		
	2019	2018	2017
Current income taxes:			
Federal	\$ (423)	\$ (416)	\$ (1,533)
State	(59)	(131)	(42)
Foreign	—	0	6
Total current income taxes	(482)	(547)	(1,569)
Deferred income taxes:			
Federal	34	(6)	(477)
State	—	—	297
Foreign	—	—	—
Total deferred income taxes	34	(6)	(180)
Total income tax provision	\$ (448)	\$ (553)	\$ (1,749)

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, 2019, 2018 and 2017 is as follows:

	Years Ended December 31,		
	2019	2018	2017
Income tax expense at statutory rate	9.3%	9.3%	9.3%
State income tax, net of federal benefit	(2.1)%	0.7%	0.3%
Nondeductible expenses	(0.1)%	0.0%	0.0%
Foreign rate differential	2.0%	(0.4)%	(2.5)%
Statutory to US GAAP permanent differences	0.1%	1.0%	1.8%
Stock-based compensation	(2.0)%	1.4%	(2.9)%
Impact of deferred rate change	(12.2)%	0.0%	0.0%
Research credits	(5.2)%	1.8%	0.8%
Change in valuation allowance	10.9%	(14.1)%	(9.4)%
Effective income tax rate	<u>0.7%</u>	<u>(0.3)%</u>	<u>(2.6)%</u>

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,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	\$ 31,496	\$ 25,418
Accruals and reserves	2,868	1,816
Operating lease liabilities	14,214	—
Deferred Rent	—	3,300
Other deferred tax assets	28	51
Stock-based compensation	5,217	2,871
Deferred revenue	(20)	3,264
Research credit	7,150	3,322
Total deferred tax assets	60,953	40,042
Less valuation allowance	(45,913)	(36,208)
Net deferred tax assets	15,040	3,834
Deferred tax liabilities:		
Depreciation	(3,901)	(3,785)
Operating lease assets	(11,068)	—
Intangible assets	(40)	(49)
Other deferred tax liabilities	(20)	(22)
Total deferred tax liabilities	(15,029)	(3,856)
Long term deferred taxes	<u>\$ 11</u>	<u>\$ (22)</u>

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, as of December 31, 2019 and 2018, the Company has provided a full valuation allowance against its net deferred tax assets in Switzerland, the United States and the UK for its TRACR subsidiary. The valuation allowance increased by \$9.7 million during 2019, which is primarily attributable to increases in the tax rates in Switzerland as a result of tax reform beginning January 1, 2020, partially offset by 2019 taxable income.

As of December 31, 2019, the Company had available non-U.S. net operating loss carryforwards of \$526.1 million of which \$262.3 million relate to Switzerland, \$262.3 million relate to the Canton of Zug, and \$1.5 million relate to the Company's wholly-owned subsidiary in the United Kingdom. The net operating losses generated in Switzerland and the Canton of Zug begin to expire in 2022 and the net operating losses generated in the United Kingdom can be carried forward indefinitely.

As of December 31, 2019, the Company had U.S. domestic federal research and development credit carryforwards of \$4.4 million which expire in 2039 for federal purposes, which are net of uncertain tax positions of \$3.0 million. As of December 31, 2019, the Company had U.S. domestic state research and development credit carryforwards of \$3.4 million which begin to expire in 2034, which are net of uncertain tax positions of \$2.2 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, 2019, the Company had gross unrecognized tax benefits of \$5.2 million of which \$4.8 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, 2019, 2018 and 2017, 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,		
	2019	2018	2017
Balance at beginning of year	\$ 1,595	\$ 354	\$ 163
Increases for tax positions taken during current period	2,754	1,212	178
Increases for tax positions taken in prior periods	882	29	13
Decreases for tax positions taken during current period	—	—	—
Decreases for tax positions taken in prior periods	—	—	—
Balance at end of year	<u>\$ 5,231</u>	<u>\$ 1,595</u>	<u>\$ 354</u>

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 tax years ending after December 31, 2015. Research credits generated in prior tax years that are closed for examination may still be adjusted upon future examination if they have or will be used in a future period. The Company is subject to income tax examinations by authorities in its non-U.S. jurisdictions for all years.

### 13. Selected Quarterly Financial Data (Unaudited)

The following table sets forth the Company's quarterly financial data for the two years ended December 31, 2019.

	2019			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Collaboration revenue	\$ 328	\$ 318	\$ 211,928	\$ 77,016
Total operating expenses	48,751	55,301	72,765	\$ 66,033
(Loss) income from operations	(48,423)	(54,983)	139,163	\$ 10,983
Net (loss) income	(48,408)	(53,699)	138,423	\$ 30,542
Net (loss) income per share attributable to common shareholders:				
Basic	\$ (0.93)	\$ (1.01)	2.52	\$ 0.53
Diluted	\$ (0.93)	\$ (1.01)	\$ 2.40	\$ 0.51
Weighted-average common shares outstanding used in net (loss) income per share attributable to common shareholders:				
Basic	52,093,208	53,188,041	54,829,057	57,395,839
Diluted	52,093,208	53,188,041	57,598,901	60,233,927
	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 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

#### 14. Related Party Transactions

##### *Casebia*

Prior to the termination of the joint venture, Casebia was a related party under ASC 850, *Related Party Disclosures* (“ASC 850”). Refer to Note 7, “*Joint Venture with Bayer Healthcare LLC.*”

##### *Vertex*

In the fourth quarter of 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. As of July 2, 2019, upon becoming owners of record of less than 10% of the voting interest of the Company, Vertex was no longer a related party under ASC 850. Refer to Note 7, “*Agreements with Vertex Pharmaceuticals Incorporated and certain of its subsidiaries.*”







## 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. Simeon J. George**  
Chief Executive Officer and President,  
S.R. One

**John T. Greene**  
Executive Vice President and Chief  
Financial Officer, Discover Financial  
Services

**Dr. Katherine A. High**  
Former Co-founder, President and  
Head of Research & Development,  
Spark Therapeutics

## TRANSFER AGENT AND REGISTRAR

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Company, LLC**  
6201 15th Avenue  
Brooklyn, NY 11219  
Phone: +1.800.937.5449  
www.amstock.com

## ANNUAL GENERAL MEETING

The Annual General Meeting of Shareholders will be **June 11, 2020** at 8:00 A.M. CET at the offices of Walder Wyss Ltd., Seefeldstrasse 123, 8008 Zurich, Switzerland. **Please read the “Important Notice Regarding COVID-19 (Coronavirus) in Switzerland” on page 6 of the Notice of Invitation to 2020 Annual General Meeting of Shareholders.**

## 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](http://www.crisprtx.com), send requests by e-mail to [ir@crisprtx.com](mailto: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 status of clinical trials, including the safety, efficacy and clinical progress of our product candidates; the therapeutic value, development, and commercial potential of CRISPR/Cas-9 gene editing technologies; the integration of Casebia Therapeutics and the expected benefits of our collaborations; 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.

## 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 Operating Officer

**Michael Tomsicek**  
Chief Financial Officer

## INDEPENDENT AUDITORS

**Ernst & Young Ltd.**  
Basel, Switzerland  
Boston, MA

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**Goodwin Procter, LLP**  
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