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, 2016

OR

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

FOR THE TRANSITION PERIOD FROM TO

Commission File Number 001-37923

CRISPR THERAPEUTICS AG

(Exact name of Registrant as specified in its Charter)

Switzerland	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Aeschenvorstadt 36 **4051 Basel, Switzerland**	
(Address of principal executive offices)	**Not Applicable** **(Zip Code)**

Registrant's telephone number, including area code: +41 61 228 7800

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

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

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

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

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

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

Indicate by check mark whether the Registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit and post such files). YES ☒ NO ☐

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

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

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

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

As of June 30, 2016, the last day of the registrant's most recently completed second fiscal quarter, there was no public market for the registrant's Common Stock. The registrant's Common Stock began trading on the NASDAQ Global Select Market on October 19, 2016. As of March 1, 2017, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $605.6 million, based on the closing price of the registrant's common stock on March 1, 2017.

As of March 1, 2017, 39,810,051 common shares were outstanding.

The Registrant was not a public company as of the last business day of its most recently completed second fiscal quarter and, therefore, cannot calculate the aggregate market value of the voting and non-voting common equity held by non-affiliates of such date.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement relating to the Annual General Meeting of Shareholders for the year ended December 31, 2016, 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, 2016, 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.

Special Note Regarding Forward-Looking Statements and Industry Data

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

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

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

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) Associated protein-9 and is a revolutionary technology for gene editing, the process of precisely altering specific sequences of genomic DNA. We are applying this technology to potentially treat a broad set of both rare and common diseases by disrupting, correcting or regulating disease-related genes. We believe that our scientific expertise, together with our gene editing approach, may enable an entirely new class of highly effective and potentially curative treatments for patients for whom current biopharmaceutical approaches have had limited success. Our most advanced programs target beta-thalassemia and sickle cell disease, two hemoglobinopathies that have high unmet medical need.

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, a director of the Max- Planck Institute for Infection Biology in Berlin. 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 foundational 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. We are pursuing a two-pronged product development strategy utilizing both *ex vivo* and *in vivo* approaches. Our most advanced programs use an *ex vivo* approach, whereby cells are harvested from a patient, treated with a CRISPR/Cas9-based therapeutic and reintroduced. We believe that an *ex vivo* approach is less technically challenging than an *in vivo* approach. We have chosen to conduct our lead programs in hemoglobinopathies given the relative ease of editing genes *ex vivo*, the significant unmet medical need associated with beta-thalassemia and sickle cell disease and the well-understood genetics of these diseases. Beyond these lead programs, we are pursuing a number of additional *ex vivo* applications, as well as select *in vivo* applications, whereby the CRISPR/Cas9 product candidate is delivered directly to target cells within the human body. Our initial *in vivo* applications will leverage well-established delivery technologies for gene-based therapeutics.

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 disease-area expertise. In particular, we established a joint venture with Bayer AG and its subsidiaries, or Bayer, in which we have a 50% interest, and a collaboration agreement with Vertex Pharmaceuticals Incorporated, or Vertex, in order to pursue specific indications where these companies have outstanding and distinctive capabilities. The significant resource commitments by our partners underscore the potential of our platform, as well as their dedication to developing transformative CRISPR/Cas9-based treatments.

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 adeno-associated virus, or 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 curative solutions 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.

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

The CRISPR/Cas9 Technology

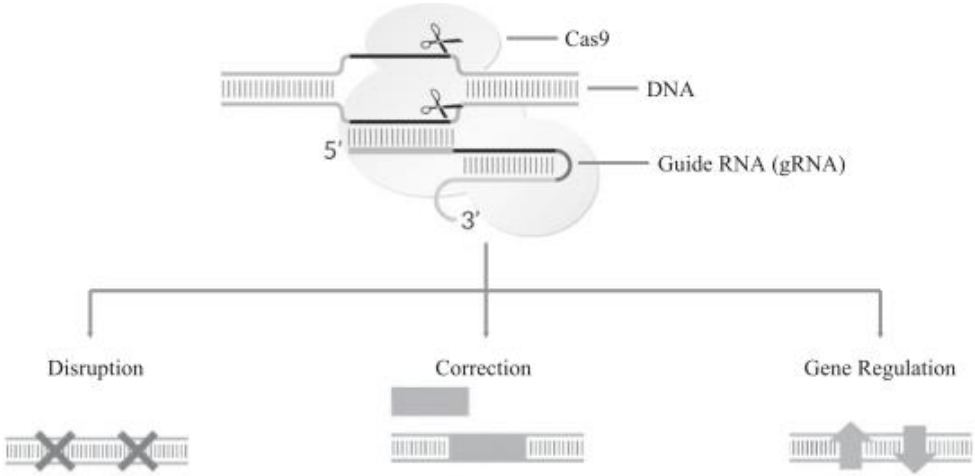
CRISPR/Cas9 evolved as a naturally occurring defense mechanism that protects bacteria against viral infections. Dr. Emmanuelle Charpentier and her collaborators elucidated this mechanism and developed ways to adapt and simplify it for use in gene editing. The CRISPR/Cas9 technology they described consists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

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

Once the DNA is cut, the cell uses naturally occurring DNA repair mechanisms to rejoin the cut ends. If a new DNA template with the correct sequence has been delivered to the cell prior to the time the DNA is cut, it will be incorporated, leading to a correction of the targeted gene, which we refer to as gene correction. Alternatively, if no DNA template is present, the cell will rejoin the two cut ends in a way that will likely lead to the disruption and inactivation of the gene, which we refer to as gene disruption.

CRISPR/Cas9 can also be adapted to regulate the activity of an existing gene without modifying the actual DNA sequence, which we refer to as gene regulation. This is accomplished using a catalytically inactive form of the Cas9 enzyme that can be directed to bind specific DNA sequences without cutting. By linking this inactive Cas9 to proteins that regulate gene function, the activity of specific genes can be either up or downregulated.

CRISPR/Cas9 gene editing

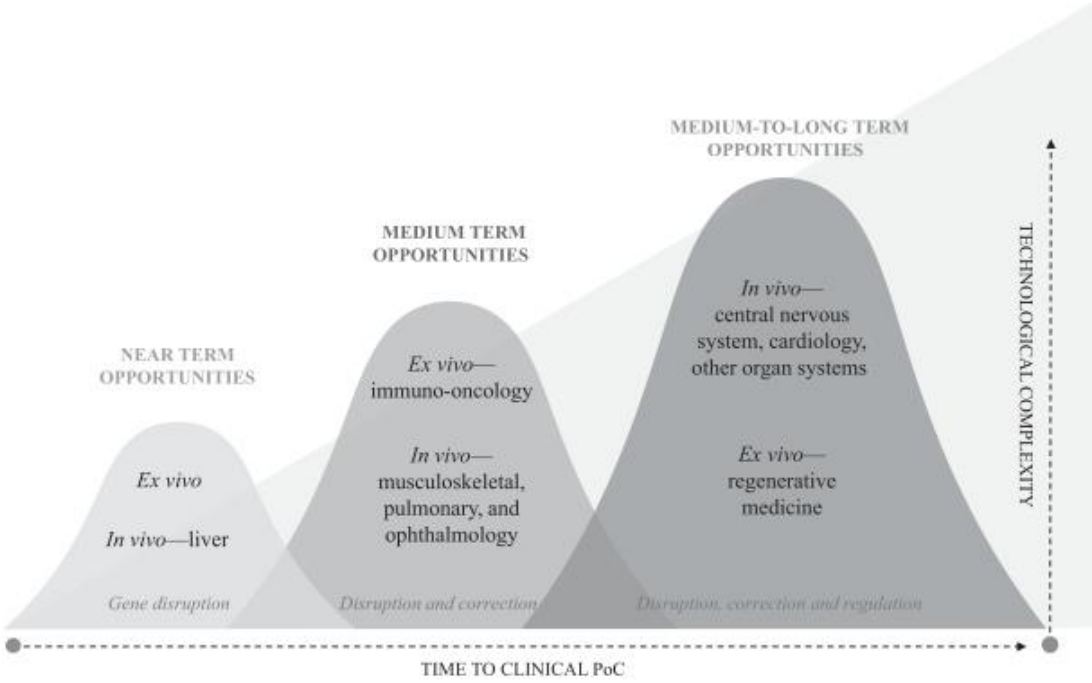


We believe that CRISPR/Cas9 is a versatile technology that can be used to either disrupt, correct or regulate genes. We intend to take advantage of the versatility and modularity of the CRISPR/Cas9 system to adapt and rapidly customize individual components for specific disease applications. Consequently, we believe that CRISPR/Cas9 may form the basis of a new class of therapeutics with the potential to treat a large number of both rare and common diseases.

Our Approach to CRISPR/Cas9 Portfolio Development

We have established a portfolio of programs by selecting disease targets based on a number of criteria, including high unmet medical need, advantages of CRISPR/Cas9 relative to alternative approaches, technical feasibility and the time required to advance the product candidate into and through clinical trials. For CRISPR/Cas9-based therapeutics, technical feasibility is primarily determined by the delivery modality and by the editing strategy required to treat the disease. The diagram below illustrates this spectrum of therapeutic applications, beginning with *ex vivo* delivery and gene disruption, progressing to *in vivo* organ systems and more sophisticated gene regulation strategies.

Strategic Progression of Our CRISPR/Cas9-Based Therapeutic Applications



We have initiated programs in three primary areas: (i) *ex vivo* programs involving gene editing of hematopoietic cells, (ii) *in vivo* programs targeting the liver and (iii) additional *in vivo* programs targeting other organ systems such as muscle and lung. By focusing our most advanced programs in *ex vivo* applications we believe we can mitigate technical and clinical risk, while also developing *in vivo* programs in parallel to fully realize the potential of our platform.

Strategic Partnerships and Collaborations

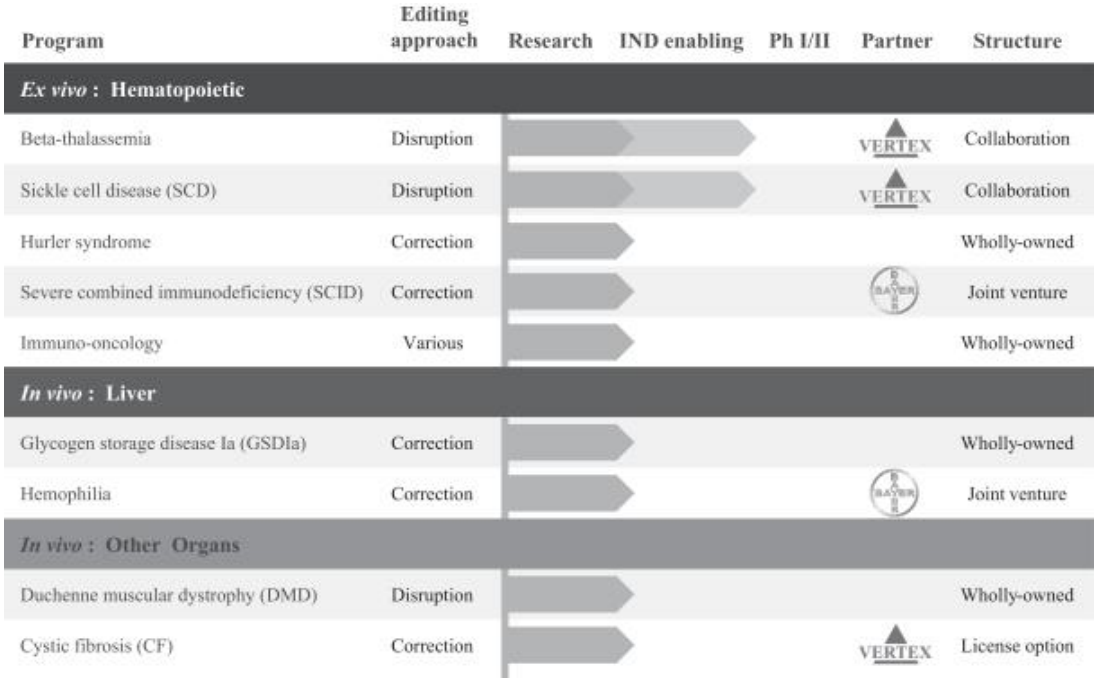
We intend to develop CRISPR/Cas9-based therapeutics both independently and in collaboration with current and potential future corporate partners. We have established collaborations with Bayer and Vertex which will provide over $400 million, subject to certain conditions, inclusive of estimated spending on funded programs, which will be used to advance the programs included in these partnerships. These significant commitments will allow us to broaden our development portfolio, as well as invest in technology enhancements and delivery technologies. As part of these collaborations, Bayer and Vertex made equity investments of $35 million and $30 million, respectively, which we believe strengthen their commitments to the growth of our company. Bayer made an additional equity investment of $35 million as a private placement concurrent with our initial public offering. We believe that the resources committed by Bayer and Vertex illustrate the potential of our CRISPR/Cas9 gene editing technology.

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

Our agreement with Vertex is a two-part collaboration. We have retained co-development and co-commercialization rights for the hemoglobinopathies program. We have also granted Vertex an option to license certain programs, with the potential to receive milestone payments and royalties.

Our Pipeline

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



Ex Vivo *Hematopoietic Program*

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 harvests stem cells directly from the patient, edits the defective gene *ex vivo*, and reintroduces those same cells back into the patient. We believe this *ex vivo* gene editing approach, which uses the patient's own cells, will provide better safety and efficacy than allo-HSCT.

Our Lead Programs—Hemoglobinopathies

Our lead programs aim to develop a single, potentially transformative CRISPR/Cas9-based therapy to treat both beta-thalassemia and sickle cell disease, or SCD. These diseases are caused by specific mutations of the beta globin gene. Beta globin is an essential component of hemoglobin, a protein in red blood cells that delivers oxygen and removes carbon dioxide throughout the body. A number of 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 to not only the lack of hemoglobin, but also as result of 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. In the most severe cases, described as beta-thalassemia major, functional beta globin is either completely absent or reduced, resulting in severe anemia. While chronic blood transfusions can be effective at addressing symptoms, they often lead to iron overload, progressive heart and liver failure, and eventually death. Patients with mild forms of beta-thalassemia may experience some mild anemia or even be asymptomatic.

The total worldwide incidence of beta-thalassemia is estimated to be 60,000 births annually, the total prevalence in the United States and the European Union is estimated to be approximately 19,000 and there are over 200,000 people worldwide who are alive and registered as receiving treatment for the disease.

Limitations of current treatment options

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

Sickle Cell Disease

Overview

Sickle cell disease is an inherited disorder of red blood cells resulting from a 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 million to 25 million people worldwide with the disease. In the United States, the total prevalence is estimated to be 100,000 individuals.

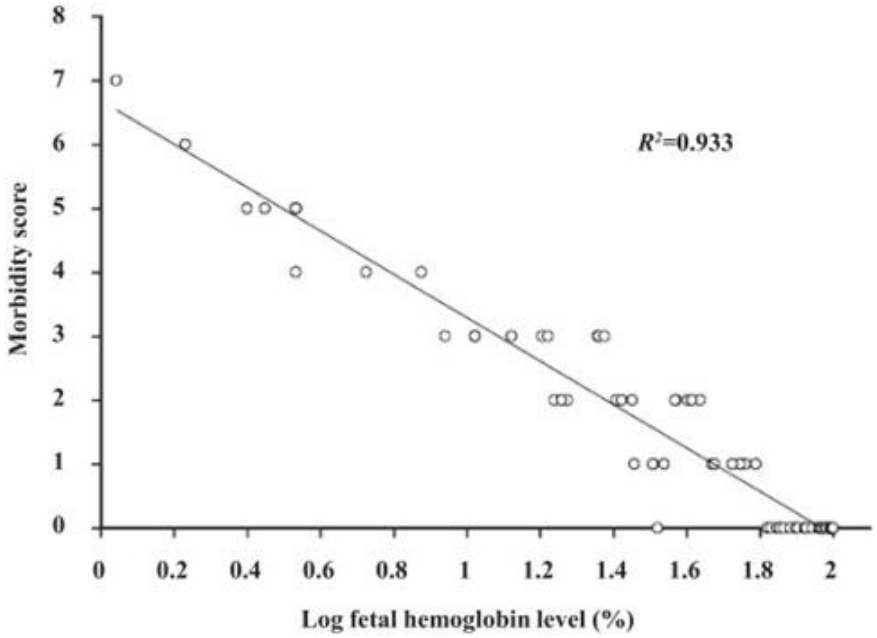
Limitations of current treatment options

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

Our Gene Editing Approach

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



We are using our CRISPR/Cas9 platform to mimic the same DNA sequence changes that occur naturally in HPFH patients. We plan to isolate patients' hematopoietic stem cells, which differentiate into red blood cells, treat these cells *ex vivo* with a CRISPR/Cas9 product candidate to edit their DNA to upregulate the expression of the gamma globin protein and reintroduce the edited cells back into the patients. We believe that the genetically modified stem cells will give rise to red blood cells that contain HbF and significantly reduce the severity of the symptoms associated with these two diseases.

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 deletion strategy involved, 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.

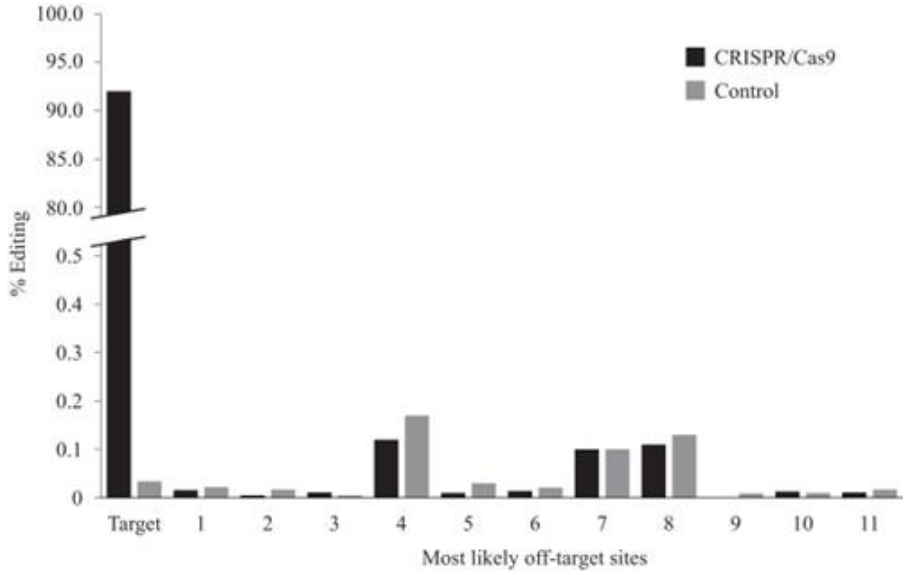
We believe our CRISPR/Cas9 gene editing strategy may have significant advantages over other gene therapies in development for the treatment of hemoglobinopathies. For example, lentivirus-based treatments involve a random integration of one or more copies of the globin gene throughout the genome. The 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. In addition, with each random integration, a mutation may be created, which may have an associated safety concern, including the potential to cause cancer.

Preclinical Data

We are progressing toward initiating clinical trials for our hemoglobinopathy programs. The first step in this process involves selecting the specific gene editing strategy and RNA guides we will use in our product candidates. We are applying our high-throughput target evaluation process to test a number of these approaches, and ultimately select RNA guides with the highest editing rate of the globin genes and the greatest effect on HbF expression. Using our high-throughput guide screening platform, we have been able to identify guide RNAs that allow editing of hematopoietic stem cells at specific locations in the genome with greater than 90% efficiency.

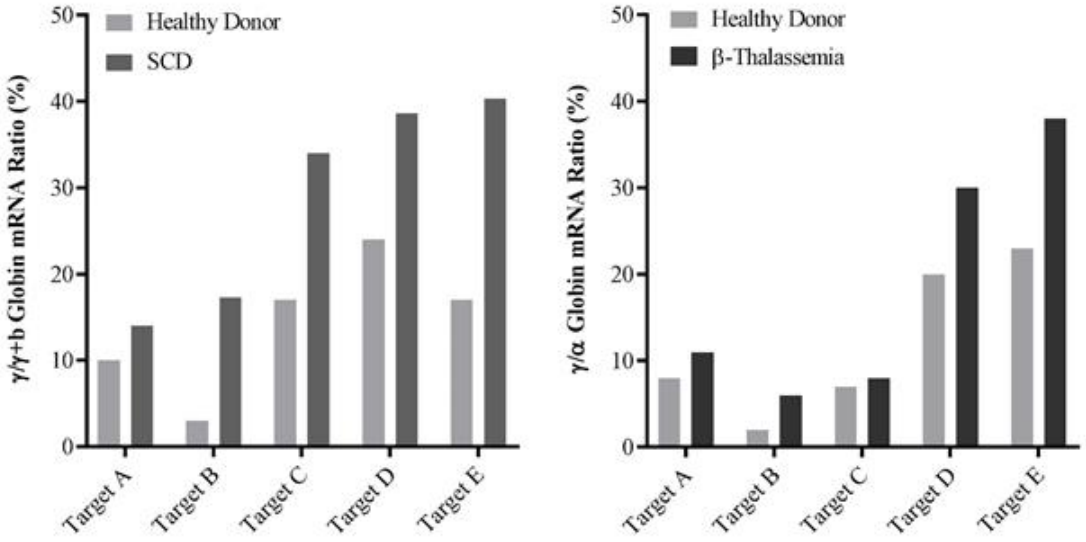
In addition to selecting guide RNAs with the highest cutting activity, we also screen our guide RNAs for off-target effects, or the introduction of cuts in DNA at locations other than the target sequence. To do this, we use bioinformatics to predict the most likely sites of off-target cuts, then test for cuts at these locations. The example guide RNA analysis shown below illustrates that we are able to identify guide RNAs that cut very efficiently at the target sites but show no off-target activity above control levels, even at sites where off-target activity is most likely to occur. We also test our lead candidates for any unlikely off-target effects using genome sequencing before advancing them for use as therapeutics.

Example guide RNA analysis



There are multiple naturally occurring genetic variants that lead to HPFH and which could form the basis of our product candidate. We have used CRISPR/Cas9 to recreate a number of these variants and tested their ability to upregulate HbF. The figure below shows the level of HbF upregulation, resulting from the recreation of five different genetic variants in hematopoietic stem cells from sickle cell and beta thalassemia patients using CRISPR/Cas9. Additionally, we have measured the level of gamma globin protein produced in these variants, to confirm the upregulation of HbF. We believe that at least two of these, named "Target D" and "Target E", may result in potentially curative levels of HbF if successfully introduced into patients with beta-thalassemia and SCD.

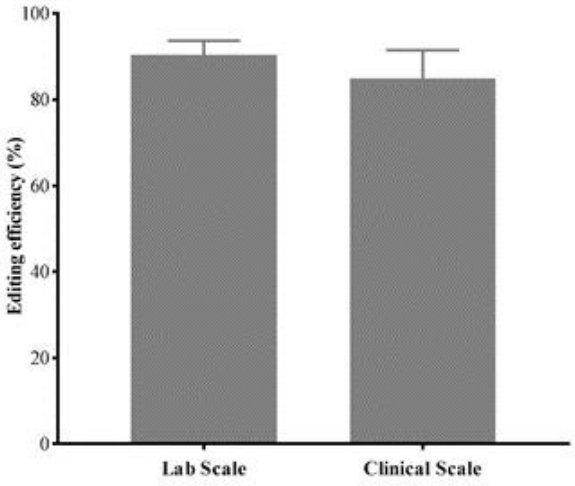
Ability of different gene targets to drive HbF production



To date, we have identified guide RNAs that perform the desired gene edits with very high efficiency, result in high levels of HbF production in cells and show no detectable evidence of off-target effects. As we continue to advance our hemoglobinopathies programs to the clinic, we are in the process of evaluating the ability of edited hematopoietic stem cells to engraft and persist in mice. Our initial engraftment studies show that the edited cells retain their ability to engraft and repopulate in immuno-compromised mice. Additionally, a subset analysis of the edited hematopoietic stem cells shows that all subsets of stem cells including the long-term repopulating stem cells are edited at high rates. These studies will also assess the ability of the edited cells to home the marrow and differentiate. Before entering clinical trials, we will also perform longer-term studies in mice to ensure there are no undesirable consequences caused by the gene edited cells.

We have also made significant progress in developing a GMP-compliant process for editing these cells in a GMP-compliant facility. We have completed multiple clinical-scale runs and analyzed the cells to show that we can achieve high editing efficiency at clinical scale with no significant change in viability of the edited cells (figure below). We have also begun toxicology studies in mice, which will utilize the edited cells manufactured in this GMP-compliant facility.

Comparison of editing efficiency at lab and clinical scales



Hurler Syndrome

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

There are two common approaches to treating mucopolysaccharide diseases: enzyme replacement therapy and allo-HSCT. Enzyme replacement therapy, or ERT, does not adequately address the symptoms of Hurler syndrome because it cannot cross the blood-brain barrier to address the severe neurologic symptoms associated with this disease. While allo-HSCT can be effective in treating the disease, it is associated with significant morbidity and mortality, and not all patients are able to find suitable donors. Even when a match is found, the delay between diagnosis and treatment often results in significant irreversible disease progression. Our approach is to introduce a functional copy of the IDUA gene into a patient's own hematopoietic cells using *ex vivo* CRISPR/Cas9 gene editing, before returning them to the patient. We believe that using a patient's own cells rather than those from a donor will eliminate a potentially lengthy search for an appropriate donor, allowing us to intervene at an earlier point and avoid the significant risks associated with allo-HSCT.

Severe Combined Immunodeficiency Disease

Severe combined immunodeficiency disease, or SCID, is a disease in which the patient's immune system is compromised and cannot fight off infections. These patients are identified early in life because they often suffer from recurrent severe respiratory infections, which can be life-threatening in the absence of a functioning immune system. There are multiple underlying causes of SCID, and in one particularly severe form, a gene called RAG1 is mutated. Mutations in RAG1, a gene that plays a critical role in the process of antibody generation, prevent normal development of the patient's immune system, resulting in an absence of B-cells, a type of white blood cell. The worldwide incidence of SCID is estimated to be one in 58,000 births, with the RAG1 mutation associated form accounting for approximately 15% of patients.

Currently, the only curative therapy for this potentially fatal disorder is allo-HSCT, which carries a high risk of complications. Gene therapies for SCID insert copies of a replacement gene randomly into the genome, potentially resulting in unwanted mutations. The risks associated with this type of gene therapy were underscored in a clinical trial for another variant of SCID in which five out of twenty patients developed leukemia. We believe that the precise correction of the RAG1 gene with CRISPR/Cas9 will bring benefit to these patients while minimizing the risk of leukemia associated with gene therapy. Considering corrected cells proliferate faster than non-corrected cells, we believe that a small number of corrected cells reintroduced into the patient could provide a therapeutic benefit and in time, compensate for the defective cells. With our *ex vivo* approach, we believe we can attain sufficient levels of correction to generate the desired therapeutic benefit. Our Casebia joint venture with Bayer HealthCare will lead development of our SCID program, and leverage Bayer HealthCare's expertise in hematologic disorders.

Future Development Opportunities

Engineered Cell Therapies For Cancer Immunotherapy

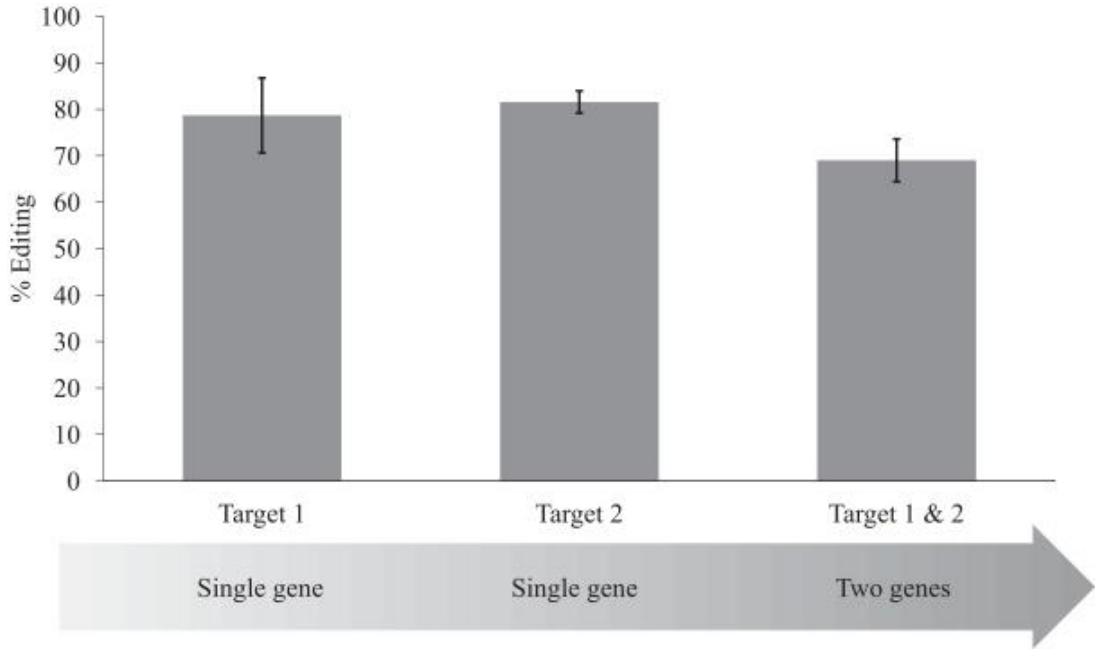
Over the past several years, interest in the oncology community has centered on immunotherapy, or treatments that harness a patient's own immune system to attack cancer cells. Engineered cell therapy is one such immunotherapy approach, in which immune system cells such as T-cells and natural killer, or NK, cells are genetically modified to enable them to recognize and attack tumor cells.

Engineered cell therapy has demonstrated encouraging clinical results and shown the potential to 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, using conventional techniques. This approach to drug development is both inefficient and cost-prohibitive. Additionally, these versions of engineered cell therapies appear limited in their ability to treat solid tumors. These products have also demonstrated sub-optimal safety profiles, including overstimulation of the immune system, occasionally resulting in death.

We are utilizing CRISPR/Cas9 to create an "off-the-shelf" cell therapy product candidate, overcoming the inefficiency and cost of creating a unique product for each patient. In addition to delivering a gene for an engineered receptor to target the tumor, creating such a product would require simultaneous disruption of several genes in order to prevent off-target immune responses. We have initial results demonstrating that this type of "multiplexed" editing can be achieved with high efficiency using CRISPR/Cas9. We are also using our platform to make other improvements such as disruption checkpoint inhibitor genes to overcome solid tumor suppression, and disrupting other genes to improve the safety profile.

We expect that the cellular engineering strategies that are ultimately successful in cancer immunotherapy 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 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. In contrast, CRISPR/Cas9 can efficiently make multiple edits using a single Cas9 protein and multiple small guide RNA molecules. The example below demonstrates the ability of CRISPR/Cas9 technology to edit two different genes in human primary T-cells with an efficiency rate similar to that of editing just one gene.

Multiplexed editing of human primary T-cells using CRISPR/Cas9



Vertical lines in each bar show the mean ± standard error from multiple experiments.

Given the potential for CRISPR/Cas9 in immunotherapy, we have established a separate unit focused on immunotherapy to accelerate our efforts. This group will have dedicated leadership, resources and capabilities to rapidly advance these programs.

In Vivo Programs

In parallel with our *ex vivo* programs, we are pursuing a number of *in vivo* indications which will involve delivery of CRISPR/Cas9 product candidates directly to tissues within the human body. Our initial *in vivo* applications will target the liver, leveraging well-established delivery technologies. We have also begun optimizing delivery systems to target other organ systems, including musculoskeletal and pulmonary.

Liver Diseases

We have selected liver diseases as our initial *in vivo* targets because delivery of nucleic acid therapies into the liver has been clinically established and validated delivery technologies are now available, including, but not limited to, lipid nanoparticle based delivery vehicles, or LNPs, and AAVs. 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, and have begun preclinical development for multiple indications including glycogen storage disease Ia, or GSDIa, and hemophilia. In both of these indications, evidence suggests that correction of the mutant gene in only a small percentage of liver cells may have a significant therapeutic effect, which makes the gene correction strategy feasible in these indications.

Glycogen Storage Disease Ia

Overview

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

Limitations of Current Treatment Options

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.

Our Gene Editing Approach

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 is capable of correcting 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.

Hemophilia

Overview

Hemophilia is an X-linked recessive genetic disease primarily present in male children. Our initial hemophilia program targets hemophilia B, which results from a deficiency in factor IX, an enzyme produced in the liver. Factor IX is part of the blood coagulation system, which enables blood to form clots in response to injury and bleeding. A lack of factor IX leads to an increased risk of bleeding, either spontaneously or in response to injury.

Patients with severe forms of the disease are first diagnosed at infancy, as witnessed through prolonged bleeding from simple medical procedures or through excessive bruising from simple falls. These patients have frequent spontaneous bleeding into joints and muscles, which can lead to edema, inflammation and debilitating pain. Patients with mild forms of the disease typically present as normal, and diagnosis usually follows surgery or trauma. The worldwide prevalence of hemophilia B patients is estimated to be 28,000, including over 4,000 in the United States. About half of hemophilia B cases are classified as severe based on levels of factor IX activity that are less than 1% of normal.

Limitations of Current Treatment Options

The standard of care for symptomatic patients with hemophilia B involves enzyme replacement with recombinant factor IX. Exogenous factor IX protein is administered both as a prophylaxis and during acute bleeding episodes. While considered effective, factor IX replacement therapies are invasive, inconvenient and non-curative. Until recently, hemophilia B therapy required weekly intravenous injections or infusions. While administration frequency has improved in recent years, key drawbacks of protein therapy, including fluctuations in factor IX levels, remain a significant pitfall of enzyme replacement therapies.

Our Gene Editing Approach

We believe that hemophilia B symptoms can be dramatically reduced with only a moderate restoration in factor IX activity. It has been shown that patients with more than 5% of normal factor IX activity have milder forms of the disease and may not present symptoms in the absence of trauma or surgery. This observation implies that in patients with severe forms of the disease, restoration of factor IX activity to a level of 5% or more of normal may be clinically meaningful.

The correction of a mutant factor IX gene with CRISPR/Cas9 leverages endogenous regulation via correction of the gene at its native location within the genome. As a result, we believe it may represent a superior way to treat hemophilia B patients, relative to other gene therapy approaches that insert the correct gene at a random location in the genome. Our hemophilia program will be developed within the Casebia joint venture, leveraging Bayer's expertise in this disease area together with our gene editing expertise.

Other Organs

We intend to pursue select *in vivo* programs targeting diseases of other organ systems such as Duchenne muscular dystrophy, or DMD, and cystic fibrosis, which have significant patient populations with high unmet medical needs, and we believe are well suited for a CRISPR/Cas9 gene editing system. For cystic fibrosis, or CF, we are working with Vertex, a global leader with extensive disease area expertise. We are working internally as well as through third-party collaborations to optimize viral and non-viral delivery technologies to overcome the delivery challenges to these organ systems.

Duchenne Muscular Dystrophy

Overview

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

There is currently one approved disease-modifying therapy in the United States for the treatment of DMD in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping, which affects about 13% of the population with DMD. There is currently no approved disease-modifying therapies in the United States for the treatment of BMD. Our gene-based therapeutic approach in development to treat DMD involves the use of oligonucleotides to promote exon skipping over the mutations that otherwise would result in truncated dystrophin synthesis. While exon skipping has demonstrated promising results in limited settings, larger clinical trials of this approach have suggested only modest efficacy. In addition, delivering sufficient levels of oligonucleotides requires repeated administration and presents challenges to treating DMD.

Our Gene Editing Approach

We are pursuing multiple approaches to developing therapies for DMD. Our first approach is to deliver CRISPR/Cas9 directly to muscle cells in patients to delete the defective exons in the dystrophin gene. The goal of this approach is to allow the gene to regain some functional capacity and produce enough dystrophin protein to diminish the more severe symptoms of DMD to resemble the milder form of the disease known as BMD. We believe that currently available technology is capable of delivering the CRISPR/Cas9 into muscle cells, and together with the relatively high efficiency of exon deletion using the CRISPR/Cas9 system, we will be able to move this program into clinical testing.

We also plan to develop an *ex vivo* cell therapy product candidate for DMD. We will derive stem cells from patient tissues and modify them *ex vivo* using our CRISPR/Cas9 technology to correct the disease causing mutations. These corrected stem cells will then be differentiated into muscle precursor cells and reintroduced into patient tissues. Once administered to the patients, we believe that the cells will divide and provide the patient with properly functioning muscle fibers with corrected copies of the dystrophin gene.

In parallel, we are performing *in vitro* experiments to test the principle of dystrophin gene correction which could potentially be curative. Prior studies in mice and humans have indicated that dystrophin levels as low as 4 to 15% of normal are sufficient to ameliorate symptoms, suggesting that even a partial restoration of dystrophin levels would be therapeutically beneficial.

Cystic Fibrosis

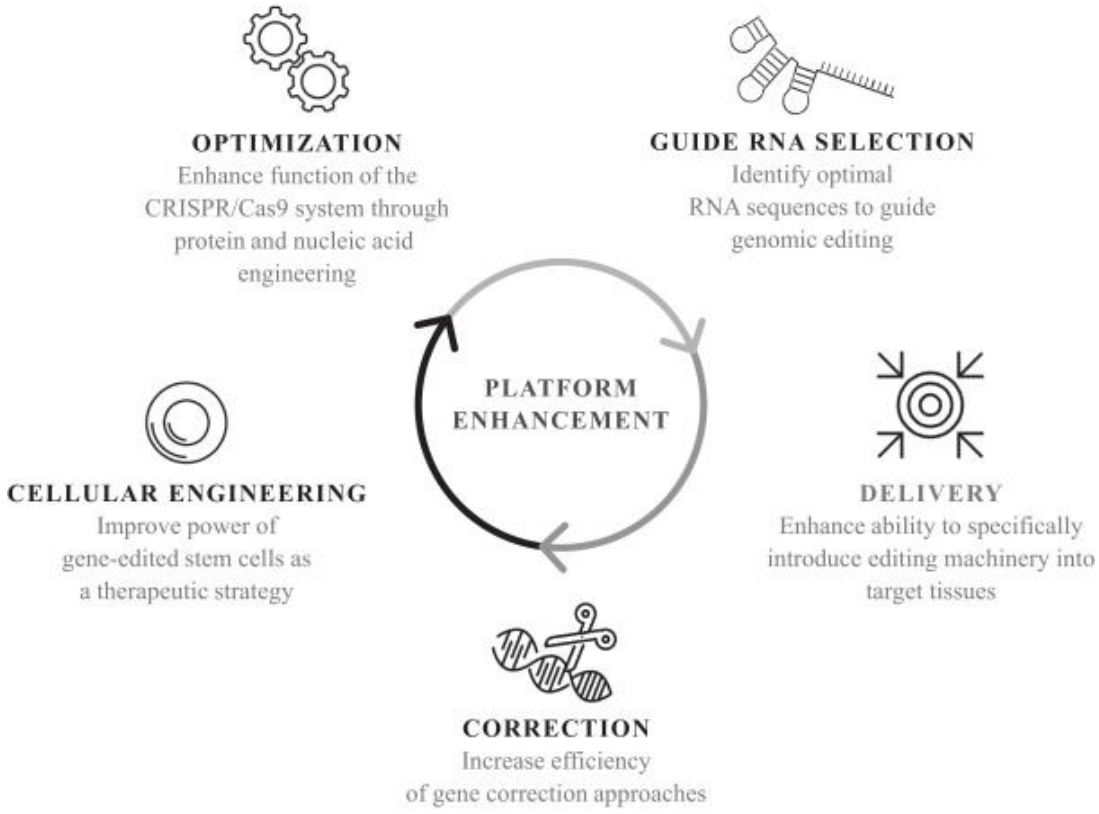
Cystic fibrosis is a progressive disease caused by mutations in the cystic fibrosis transmembrane regulator, or CFTR, gene resulting in the loss or reduced function of the CFTR protein. Although there are several different mutations associated with CF, approximately 70% of CF patients have the same mutation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

CF is an orphan disease that affects an estimated 70,000 to 100,000 patients worldwide, with a majority in the United States and Europe. The median age of death from CF in the United States in 2014 was 29 years, with most deaths resulting from respiratory failure. CF patients require lifelong treatment with multiple daily medications and hours of self-care. They often require frequent hospitalizations and sometimes even lung transplantation, which can prolong survival but is not curative.

Studies have shown that as little as 10% of normal CFTR function can ameliorate disease symptoms. Our approach is focused on using our CRISPR/Cas9 technology to correct the mutation at codon 508. Together with our collaboration partner Vertex, we believe that we will be able to deliver CRISPR/Cas9 to the lung and correct this mutation sufficiently to improve symptoms in patients with CF.

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.



Optimization of the Cas9 Protein

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 develop these.

Our research and development efforts seek to enhance a number of 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 a number of effective Cas9 versions with different properties, each of which may be best suited to a certain disease area or type of genetic editing.

Guide RNA Selection

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 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.

We are building a guide RNA selection process that combines bioinformatics and experimental assays to enable the screening of over 10,000 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, whole genome sequencing 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.

Delivery

Delivery of CRISPR/Cas9 into cells is a critical step to ensure that the therapeutic will be effective. We can deliver our Cas9 in the form of protein, DNA or RNA, allowing us to tailor the delivery format to the target tissue. For our *ex vivo* programs, we are using both protein and mRNA forms of Cas9 delivered via electroporation, which is the process of using a pulse of electricity to briefly open the pores of the cell membrane. For *in vivo* delivery to cells and organs in the patient we are evaluating and testing a variety of technologies that include LNPs and AAVs, as well as other delivery methods, before selecting the specific versions for use in our product candidates. In addition, we are collaborating externally to develop next-generation delivery technologies that will allow us to access organ systems that are less accessible today. Some of this activity may be done through our Casebia joint venture with Bayer HealthCare which provides us access to supporting technologies such as delivery vehicles.

Correction

While gene correction is achievable today using CRISPR/Cas9, it is more difficult and has lower efficacy than the more straightforward gene disruption strategy. Our initial gene correction programs target diseases in which therapeutic efficacy can be achieved through correction of only a small percentage of cells, while other potential indications may require correction of a significantly higher percentage of cells. We are working with our collaborators to increase the efficiency of gene correction in order 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. In addition, we are advised by Dr. Stephen Elledge, Professor of Genetics at Harvard Medical School, who is an expert in DNA damage and repair, to explore ways to optimize the cellular processes involved in the correction process. We are also collaborating more broadly with leaders in the DNA repair field, to explore other approaches to optimize correction rates.

Cellular Engineering

Many *ex vivo* applications of our technology use a strategy of editing stem cells *ex vivo* which, when returned to the patient, differentiate into a variety of different cell types. For certain stem cell types, especially hematopoietic cells, there are well-established procedures to support this strategy. For others, these procedures are more nascent and require further development. A critical focus for us is to improve the efficacy, efficiency and safety of the *ex vivo* cell collection, manipulation and administration process for a variety of stem cell types. We are evaluating technologies to improve mobilization of a patient's stem cells, to maintain viability of the harvested cells, and to improve the ability of these cells to engraft into a patient's body. Both in our own laboratories and through our academic partnerships, we intend to perform additional research to optimize these parameters for each organ system.

Intellectual Property

We strive to protect and enhance the proprietary technologies that we believe are important to our business by seeking patents to cover our platform technology, which consists of the in-licensed intellectual property of Dr. Emmanuelle Charpentier described below, including compositions of matter and their therapeutic uses. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for our technology, our ability to defend and enforce our intellectual property rights and our ability to operate without infringing any valid and enforceable patents and proprietary rights of third parties.

In-Licensed Intellectual Property

In April 2014, pursuant to an exclusive license with Dr. Emmanuelle Charpentier, or the Charpentier License, we licensed from Dr. Charpentier certain rights to a family of patent applications relating to compositions of matter, including additional CRISPR/TRACR/Cas9 complexes, and methods of use, including their use in targeting or cutting DNA. The Charpentier 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 the Charpentier License, please see "Business – CRISPR License with Dr. Emmanuelle Charpentier."

This family of patent applications includes two granted patents in the United Kingdom and pending patent applications in the United States, Europe, Canada, Mexico, Australia and other selected countries in Central America, South America, Asia and Africa. The granted patents in the United Kingdom and any other patents that may ultimately issue in this patent family are expected to expire in 2033, not including any applicable extensions.

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

In January 2016, the U.S. Patent and Trademark Office, or USPTO, declared an interference between one of the pending U.S. patent applications in this family and twelve issued U.S. patents owned jointly by the Broad Institute and Massachusetts Institute of Technology and, in some instances, the President and Fellows of Harvard College, which we refer to individually and collectively as Broad. The interference was redeclared in March 2016 to add a U.S. patent application owned by Broad. An interference is a proceeding conducted at the USPTO by the Patent Trial and Appeal Board, or PTAB, to determine which party was the first to invent subject matter claimed by at least two parties. There are currently two parties to this interference. The USPTO designated Dr. Emmanuelle Charpentier, California and Vienna collectively as "Senior Party" and designated Broad as "Junior Party." 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 particular, the Junior Party's claims in the interference were all limited to uses in eukaryotic cells, while the Senior Party's claims in the interference were not limited to uses in eukaryotic cells but included uses in all settings. Either party can appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In parallel, either party can also pursue existing or new patent applications in the U.S. and elsewhere. Going forward, either party as well as other parties could seek a new interference related to the uses of the technology in eukaryotic cells or other aspects of the technology, and any existing or new patents could be the subject of other challenges to their validity of enforceability. If there is a second interference, either party could again appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In any case, it may be years before there is a final determination on priority. Pursuant to the terms of the license agreement with Dr. Charpentier, we are responsible for covering or reimbursing Dr. Charpentier's patent prosecution, defense and related costs associated with our in-licensed technology. 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."

On December 15, 2016, we entered into a Consent to Assignments, Licensing and Common Ownership and Invention Management Agreement, or the IMA, with California, Vienna, Dr. Charpentier, Intellia, Caribou, ERS Genomics Ltd., or ERS, and TRACR. Under the IMA, California and Vienna retroactively consent to Dr. Charpentier's licensing of her rights to the CRISPR/Cas9 intellectual property, pursuant to the Charpentier License, to us, our wholly-owned subsidiary TRACR, and ERS, in the United States and globally. The IMA also provides retroactive consent of co-owners to sublicenses granted by us, TRACR and other licensees, prospective consent to sublicenses they may grant in future, retroactive approval of prior assignments by certain parties, and provides for, among other things, (i) good faith cooperation among the parties regarding patent maintenance, defense and prosecution, (ii) cost-sharing arrangements, and (iii) notice of and coordination in the event of third-party infringement of the subject patents and with respect to certain adverse claimants of the CRISPR/Cas9 intellectual property. Unless earlier terminated by the parties, the IMA will continue in effect until the later of the last expiration date of the patents underlying the CRISPR/Cas9 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

We also own over 80 families of patent applications relating to our platform technology or its therapeutic applications. These patent applications are currently pending in the United States and in some cases in other countries, and we may elect to pursue additional related applications internationally. Any patents that ultimately issue from these patent applications may begin to expire in 2034.

Patent Assignment Agreement

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

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

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

License Agreements

CRISPR License With Dr. Emmanuelle Charpentier

In April 2014, we entered into a license agreement, or the Charpentier License Agreement, with Dr. Emmanuelle Charpentier, one of our co-founders, pursuant to which we received an exclusive license under Dr. Charpentier's joint ownership interest a family of patent applications relating to CRISPR/TRACR/Cas9 complexes and their use in targeting or cutting DNA, which we refer to as the Patent Rights, 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 granted us an exclusive, worldwide, royalty-free sublicense, including the right to sublicense, to research, develop, produce, commercialize and sell therapeutic products relating to the CRISPR Field which incorporate any intellectual property that TRACR Hematology Ltd., our majority-owned subsidiary, or TRACR, develops under its license with Dr. Charpentier. In turn, we granted to Dr. Charpentier an exclusive license with the obligation to sublicense to TRACR any intellectual property we develop under the license with Dr. Charpentier for treatment and prevention of hemoglobinopathy in humans, including, without limitation, sickle cell disease and thalassemia.

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

Unless terminated earlier, the term of the Charpentier License Agreement will expire on a country-by-country basis, upon the expiration of the last to expire valid claim of the Patent Rights in such country. We have the right to terminate the agreement at will upon 60 days' written notice to Dr. Emmanuelle 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 Rights.

TRACR License With Dr. Emmanuelle Charpentier

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

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

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

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

Bayer Joint Venture

In December 2015, we entered into a Joint Venture Agreement, or the JV Agreement, with Bayer HealthCare LLC, or Bayer HealthCare, to create Casebia Therapeutics LLP, or Casebia, to discover, develop and commercialize new therapeutics for genetically linked diseases, including blood disorders, blindness and heart disease. At the closing of the transactions contemplated by the JV Agreement in March, 2016, or the Closing, we contributed $0.1 million to Casebia and we and certain of our affiliates entered into an intellectual property contribution agreement with Casebia, or the CRISPR IP Contribution Agreement, as discussed below, exclusively licensing our CRISPR/Cas technology to Casebia for the purpose of developing and commercializing therapeutic products in certain specified fields, or the Casebia Fields. Bayer HealthCare contributed an initial amount of $45 million at the Closing to Casebia and is committed to contribute up to an additional $255 million in additional funds over time to fund the operations of Casebia, subject to the conditions and procedures discussed below. We and Bayer HealthCare each hold a 50%, non-transferable interest in Casebia. Casebia subleases a portion of our Cambridge office for its initial operations.

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

Governance

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

Budget And Funding

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

Non-Competition

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

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

Termination

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

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

IP Contribution Agreement With Casebia

As part of our contribution to Casebia, in March 2016, we and certain of our affiliates entered into the CRISPR IP Contribution Agreement with Casebia. Pursuant to the CRISPR IP Contribution Agreement, we and certain of our affiliated entities granted Casebia an exclusive, worldwide, fully paid-up, royalty-free license, including the right to sublicense, to the use of our CRISPR/Cas technology to research, develop, produce, commercialize and sell products in the Casebia Fields. As partial consideration for the license, Casebia is required to pay us an aggregate amount of $35 million for a technology access fee, consisting of an upfront payment of $20 million, which was paid at the closing of the JV Agreement in March 2016, and another payment of $15 million when we obtain specified intellectual property rights relating to our CRISPR/Cas9 technology outside of the United States, which was paid in December 2016 upon the signing of the IMA. The CRISPR IP Contribution Agreement also contains license grants from Casebia to us to various forms of intellectual property developed or in-licensed by Casebia. The CRISPR IP Contribution Agreement will terminate simultaneously with the termination of the JV Agreement, subject to survival of certain licenses granted during the term, including licenses granted pursuant to an exercise of an option pursuant to the Option Agreement.

Option Agreement With Bayer

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

Collaboration Agreement With Vertex

On October 26, 2015, we entered into a Strategic Collaboration, Option and License Agreement, or the Collaboration Agreement, with Vertex Pharmaceuticals, Incorporated and Vertex Pharmaceuticals (Europe) Limited, together, Vertex. Pursuant to the Collaboration Agreement, we agreed to provide technology and options to obtain licenses relating to our CRISPR/Cas technology to Vertex in exchange for a $75 million upfront payment. In connection with the Collaboration Agreement, Vertex also made a $30 million equity investment in us.

Under the Collaboration Agreement, Vertex has the option to exclusively license treatments for up to six collaboration targets that emerge from the four-year research collaboration under certain of our platform and background intellectual property to develop, manufacture, commercialize, sell and use therapeutics directed to each such collaboration target. For any non-hemoglobinopathies targets in-licensed for development, Vertex will pay future development, regulatory and sales milestones of up to $420 million per target, as well as royalty payments in the single digits to low teens on future sales of a commercialized product candidate. The milestone and royalty payments are each subject to reduction under certain specified conditions set forth in the Collaboration Agreement. For these therapies, Vertex is solely responsible for all research, development, manufacturing and global commercialization activities.

However, specifically for hemoglobinopathies targets, if Vertex exercises one or more of its six options on a hemoglobinopathy target, including targets for sickle cell disease, we and Vertex will equally share all development costs and sales expenses. If a hemoglobinopathy target is successfully developed, we would be the lead party responsible for commercialization efforts in the United States and Vertex would be the lead party responsible for commercialization efforts outside the United States. The profits from the sales of any hemoglobinopathies products will be equally shared by Vertex and us.

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

Either party can terminate the Collaboration Agreement upon the other party's material breach, subject to specified notice and cure provisions. Vertex also has the right to terminate the Collaboration Agreement for convenience at any time upon 90 days' written notice prior to any product receiving marketing approval and upon 270 days' notice after a product has received marketing approval. In the event we and Vertex make a filing under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, for a collaboration target and such filing is not cleared within a specified time after such filing, the Collaboration Agreement will terminate with respect to that target. We may also terminate the Collaboration Agreement in the event Vertex challenges any of our patent rights.

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

License Agreement with Anagenesis

On June 7, 2016, we entered into a license agreement with Anagenesis Biotechnologies SAS, or Anagenesis, pursuant to which we received an exclusive worldwide license to Anagenesis' proprietary technology for all human based muscle diseases. We plan to initially use these rights to advance our research and product development efforts for our Duchenne muscular dystrophy program. Pursuant to the license agreement, we made a one-time upfront payment of $0.5 million to Anagenesis and are required to pay Anagenesis up to $89.0 million upon the achievement of future clinical, regulatory and sales milestones for each of the first allogeneic and autologous licensed products developed pursuant to the license agreement, as well as low single digit royalty payments on future sales of commercialized product candidates.

We can terminate the license agreement at any time upon 30 days' written notice. Either party may also terminate the license agreement upon the other party's material breach, subject to specified notice and cure provisions. Either party may terminate the license agreement in the event the other party becomes subject to specified bankruptcy, winding up or similar circumstances. Absent early termination, the license agreement will continue until the expiration of our payment obligations on a country-by-country basis.

Manufacturing

We currently have no commercial manufacturing or cell processing capabilities. We are working to establish manufacturing processes for both *in vivo* and *ex vivo* CRISPR/Cas9-based therapies and have established relationships with third-party manufacturers with capabilities to manufacture the necessary human cells, Cas9 and guide RNAs in accordance with current Good Manufacturing Practices, or cGMP. We plan to continue to rely on qualified third-party organizations to produce or process bulk compounds, formulated compounds, viral vectors or engineered cells for IND-supporting activities and early stage clinical trials. We expect that commercial quantities of any compound, vector, or engineered cells that we may seek to develop will be manufactured in facilities and by processes that comply with FDA and other regulations. At the appropriate time in the product development process, we will determine whether to establish manufacturing facilities or continue to rely on third parties to manufacture commercial quantities of any products that we may successfully develop. Outside of the United States and Europe, where appropriate, we may elect in the future to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products. In certain instances, we may consider building our own commercial infrastructure.

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

Competition

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

We compete in the segments of the pharmaceutical, biotechnology, and other related markets that utilize technologies encompassing genomic medicines to create therapies, including gene editing and gene therapy. There are additional companies that are working to develop therapies in areas related to our research programs.

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

There are additional companies developing therapies using additional gene-editing technologies, including TALENs, meganucleases, and zinc finger nucleases. The companies developing these additional gene-editing technologies include bluebird bio, Cellectis, Poseida Therapeutics, Precision Biosciences, and Sangamo Biosciences. Additional companies developing gene therapy products include Abeona Therapeutics, Avalanche Biotechnologies, Dimension Therapeutics, REGENXBIO, Spark Therapeutics and uniQure. In addition to competition from other gene-editing therapies or gene therapies, any products that we develop may also face competition from other types of therapies, such as small molecule, antibody, or protein therapies.

We may also face future competition from newly discovered gene editing technologies or new CRISPR-associated nucleases. While we believe that CRISPR/Cas9 will be highly effective for many therapeutic applications and are actively working to further enhance the technology, more efficient gene editing technologies may emerge. For example, recent publications by Feng Zhang, Ph.D., one of the founders of Editas Medicine, Inc. and others have elucidated a different CRISPR-associated nuclease, Cpf1, which can also edit human DNA. Some have argued that Cpf1 is superior to Cas9 for certain applications. Gene editing is a highly active field of research and new technologies, related or unrelated to CRISPR, may be discovered and create new competition.

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

If our current programs are approved for the indications for which we are currently planning clinical trials, they may compete with other products currently under development, including gene editing and gene 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 that is taking place by several companies, including us and our competitors, in the gene editing field, the intellectual property landscape is in flux and highly competitive. There may be significant intellectual property related litigation and proceedings, in addition to the ongoing interference proceedings, relating to our owned and in-licensed, and other third party, intellectual property and proprietary rights in the future.

For example, in January 2016, at our request, the USPTO declared an interference between one of the pending U.S. patent applications we licensed from Dr. Emmanuelle Charpentier and twelve issued U.S. patents, and subsequently added one U.S. patent application, owned jointly by Broad. Because our application was filed first, the USPTO designated Dr. Charpentier, California and Vienna, or Vienna, collectively as "Senior Party" and designated Broad as "Junior Party." 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 particular, the Junior Party's claims in the interference were all limited to uses in eukaryotic cells, while the Senior Party's claims in the interference were not limited to uses in eukaryotic cells but included uses in all settings. Either party can appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In parallel, either party can also pursue existing or new patent applications in the U.S. and elsewhere. Going forward, either party as well as other parties could seek a new interference related to the uses of the technology in eukaryotic cells or other aspects of the technology, and any existing or new patents could be the subject of other challenges to their validity of enforceability. In the context of a second interference or in other proceedings, a determination could be reached regarding that the Senior Party was not the first to invent, or it could be concluded that the contested subject matter is not patentable to the Senior Party and is patentable to the Junior Party, which in this case could preclude our U.S. patent applications from issuing as patents, in which case the proceedings would result in our losing the right to protect core innovations and our freedom to practice our core gene editing technology. If there is a second interference, either party could again appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In any case, it may be years before there is a final determination on priority. 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 currently involved in the interference with Dr. Emmanuelle Charpentier, California and Vienna. We are also aware of additional third parties that have pending patent applications relating to CRISPR technologies, which similarly may lead to further interference proceedings. For example, Rockefeller

University has filed a continuation application (U.S. Serial No. 14/324,960) of an application filed by the Broad that Rockefeller's employee Luciano Marraffini as co-inventor of CRISPR/Cas9 technology; Vilnius University has filed applications in the United States and in other jurisdictions (published internationally as WO2013/141680 and WO2013/142578), Harvard University has filed applications in the United States and in other jurisdictions (published internationally as WO2014/099744), and Sigma-Aldrich has filed applications in the United States and in other jurisdictions (published internationally as WO2014/089290), each claiming aspects of CRISPR/Cas9 technology based on applications claiming priority to provisional filings in 2012. Numerous other filings are based on provisional applications filed after 2012.

Both Broad and Toolgen have filed international counterparts of their U.S. applications, some of which were granted in Europe and/or other 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, if we should obtain patent grants in the U.S., Europe and other jurisdictions, these could also be the subject of oppositions or other post-grant procedures sought by third parties in order to revoke the grants or narrow the scope of granted claims. Going forward, with existing and new challenges being filed against CRISPR/Cas9 cases in the U.S., Europe and elsewhere, and considering the number of interested parties, it is reasonable to expect that patents directed to the underlying technology will continue to be the subject of ongoing disputes over at least the next several years, and potentially beyond as decisions in favor or against particular parties may be the subject of appeals.

Government Regulation

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

Licensure and Regulation of Biologics in the United States

In the United States, our candidate products would be 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 non-clinical 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 U.S. Food and Drug Administration's, or FDA's, refusal to allow an applicant to proceed with clinical testing, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, untitled or warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, and civil or criminal investigations and penalties brought by the FDA or the Department of Justice, or DOJ, or other governmental entities.

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

- preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an investigational new drug, or 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 non-clinical 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 Investigational New Drug, or IND, application. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA imposes a clinical hold based on concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects would be exposed to unreasonable and significant health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin.

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

With gene therapy protocols, if the FDA allows the IND to proceed, but the Recombinant DNA Advisory Committee, or RAC, of the National Institute of Health, or NIH, decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process.

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 international guidelines for the ethical conduct of clinical research known as good clinical practice, or GCP, and the FDA is able to validate the data from the study through an onsite inspection if the FDA deems it necessary.

Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, subject informed consent, ethical factors, and the safety of human subjects. An IRB must operate in compliance with FDA regulations. The FDA or the clinical trial sponsor may suspend or terminate a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with FDA requirements or the subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety

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

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

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

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

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

Special Regulations and Guidance Governing Gene Therapy Products

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

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

If a gene therapy trial is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, a protocol and related documentation must submitted to, and the study registered with, the NIH Office of Biotechnology Activities, or OBA, pursuant to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules 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 follow them. The NIH will convene the Recombinant DNA Advisory Committee, or RAC, a federal advisory committee, to discuss protocols that raise novel or particularly important scientific, safety or ethical considerations at one of its quarterly public meetings. The OBA will notify 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.

Finally, to facilitate adverse event reporting and dissemination of additional information about gene therapy trials, the FDA and the NIH established the Genetic Modification Clinical Research Information System, or GeMCRIS. Investigators and sponsors of a human gene transfer trials can utilize this web-based system to report serious adverse events and annual reports. GeMCRIS also allows members of the public to access basic reports about human gene transfer trials registered with the NIH and to search for information such as trial location, the names of investigators conducting trials, and the names of gene transfer products being studied.

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 non-clinical 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.

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

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

Fast Track, Breakthrough Therapy and Priority Review Designations

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

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

Second, in 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as "breakthrough therapies." A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting adverse reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months.

Accelerated Approval Pathway

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

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

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

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

Post-Approval Regulation

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

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

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences 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, 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. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. 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. To date, four biosimilar products have been approved by the FDA for use in the United States. No interchangeable biosimilars, however, have been approved. The FDA has issued several guidance documents outlining an approach to review and approval of biosimilars. Additional guidances are expected to be finalized by the FDA in the near term.

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

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

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable health regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal

products in the European Union, or EU, generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the European Medicines Agency, or EMA, or the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by the EMA or these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

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

In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new Clinical Trials Regulation (EU) No 536/2014 will become applicable no earlier than May 28, 2016. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new legislation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single entry point and strictly defined deadlines for the assessment of clinical trial applications.

Marketing Authorization

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

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

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

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

Regulatory Data Protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Periods of Authorization and Renewals

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

Regulatory Requirements after Marketing Authorization

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

Orphan Drug Designation and Exclusivity

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

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

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

Coverage, Pricing and Reimbursement

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

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

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

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

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

Healthcare Law and Regulation

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

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, or receiving remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil U.S. False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious, or fraudulent or knowingly making, using, or causing to be made or used a false record or statement to avoid, decrease, or conceal an obligation to pay money to the federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the U.S. False Claims Act;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the U.S. federal Health Insurance Portability and Accountability Act, or HIPAA, as amended by the U.S. Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations with respect to safeguarding the privacy, security, and transmission of individually identifiable information that constitutes protected health information, including mandatory contractual terms and restrictions on the use and/or disclosure of such information without proper authorization;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the U.S. Patient Protection and Affordable Care Act, as amended by the U.S. Health Care and Education Reconciliation Act, collectively the Affordable Care Act or ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the U.S. Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, and requires certain manufacturers and appliacble group purchasing organizations to report ownership and investment interests held by physicians or their immediate family members; and
- analogous laws and regulations in other national jurisdictions and states, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

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

Healthcare Reform

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

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

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

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers, and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

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, 2016 we had 93 full-time employees, 48 of whom held Ph.D. or M.D. degrees, 75 of whom were engaged in research and development, and 18 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.

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 to date through proceeds from our initial public offering, or the IPO, and concurrent private placement of our common shares, private placements of our preferred shares and convertible securities and payments received from Casebia Therapeutics, LLC pursuant to our joint venture with Bayer HealthCare LLC, or Bayer Healthcare, and our collaboration with Vertex Pharmaceuticals, Incorporated, or Vertex. Since inception, we have incurred significant operating losses. Our net loss was $23.2 million, $25.8 million, and $6.8 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016 and 2015, we had an accumulated deficit of $57.1 million and $33.9 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 current research programs and our preclinical development of product candidates from our current research programs;
- seek to identify additional research programs and additional product candidates;
- conduct IND supporting preclinical studies and initiate clinical trials for our most advanced product candidates which are from our hemoglobinopathy program targeting beta thaleassemia and sickle cell disease;
- initiate preclinical studies and clinical trials for any other product candidates we identify and choose to develop;
- maintain, expand and protect our intellectual property portfolio;
- seek marketing approvals for any of our product candidates that successfully complete clinical trials;
- further develop our gene editing technology;
- hire additional clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product candidate development;
- acquire or in-license other technologies;
- ultimately establish a sales, marketing, and distribution infrastructure to commercialize any products for which we may obtain marketing approval; and
- operate as a public company.

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

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

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

As of December 31, 2016 and 2015, we had cash of approximately $315.5 million and $156.0 million, respectively. We expect that our existing cash, including the net proceeds from our IPO and the concurrent private placement, together with anticipated research support under our joint venture with Bayer Healthcare and collaboration agreement with Vertex, will enable us to fund our operating expenses and capital expenditure requirements for 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 drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the scope, prioritization and number of our research and development programs;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of establishing and maintaining a supply chain for the development and manufacture of our product candidates;
- the success of our current joint venture with Bayer Healthcare and our collaboration with Vertex;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- the achievement of milestones or occurrence of other developments that trigger payments under any additional collaboration agreements we obtain;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the costs of fulfilling our obligations under the IMA 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 are early in our development efforts and all of our lead programs are still in preclinical or the discovery stage. 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.

The lead product candidates from our hemoglobinopathy program targeting beta-thalassemia and sickle cell disease require among other things, completion of IND supporting preclinical studies. Each of our other programs require additional discovery research and then preclinical development. All of our programs, including our hemoglobinopathy program, require clinical development, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, capacity and expertise, building of a commercial organization, substantial investment and significant marketing efforts before we generate any revenue from product sales. In addition, our product candidates must be approved for marketing by the FDA or certain other health regulatory agencies, including the 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. Similarily, 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 encounter unforeseen expenses, difficulties, complications, delays and other known and unknown circumstances. As we advance our product candidates, we will need to transition from a company with a research focus to a company capable of supporting clinical development and if successful, commercial activities. We may not be successful in such a transition.

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

Under Swiss law, we are entitled to carry forward losses we incur for a period of seven years and we can offset future profits, if any, against such losses. As of December 31, 2016, we reported tax loss carry forwards from inception through 2015 for purposes of Swiss federal direct taxes in the aggregate amount of CHF 22.0 million. Due to the accepted mixed company status (the tax ruling with respect to the mixed company status was accepted in February 2017 with retroactive effect as from 2013/2014) the tax losses available to offset future income at cantonal level amount to CHF 4.1 million. If not used, these tax losses will expire seven years after the year in which they occurred. Due to our limited income, there is a high risk that the tax loss carry forwards will expire partly or entirely. For 2016, the tax return has – in accordance with Swiss tax law – not yet been filed. Therefore, for 2016 the loss carried forward will only be claimed with filing of the tax return for the tax year 2016.

Risks Related to Our Business, Technology and Industry

We Are Early In Our Development Efforts. All Of Our Product Candidates Are Still In Preclinical Development And It Will Be Many Years Before We Or Our Collaborators Commercialize A Product Candidate, If Ever. If We Are Unable To Advance Our Product Candidates To 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 CRISPR/Cas9, gene editing technology, identifying our initial targeted disease indications and our initial product candidates. Our future success depends heavily on the successful development of our CRISPR/Cas9 gene editing product candidates including our most advanced product candidates which target beta-thalassemia and sickle cell disease. We have invested substantially all of our efforts and financial resources in the identification and preclinical development of our current product candidates. Currently, all of our product candidates including our most advanced product candidates which target beta-thalassemia and sickle cell disease are in preclinical development. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates, which may never occur. For example, our research programs, including those subject to our joint venture with Bayer Healthcare and collaboration agreement with Vertex, may fail to identify potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates, 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 plan to file our clinical trial applications, or CTAs, to begin our first clinical trial for our hemoglobinopathy program targeting beta-thalassemia in late 2017 and for our hemoglobinopathy program targeting sickle cell disease in early 2018. In each case, the filing is subject to the identification and selection of guide RNA with acceptable efficiency. Commencing this clinical trial, and any other clinical trials we may initiate, is also subject to acceptance by the FDA of our Investigational New Drug application, or IND, and finalizing the trial design based on discussions with the FDA and other regulatory authorities, including the NIH. In the event that the FDA requires us to complete additional preclinical studies or we are required to satisfy other FDA requests, the start of our first clinical trial for our hemoglobinopathy programs or any of our other programs may be delayed. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence our clinical trial or change their position on the acceptability of our 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 preclinical studies;
- sufficiency of our financial and other resources to complete the necessary preclinical studies and clinical trials;
- 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;
- a positive recommendation of the Recombinant DNA Advisory Committee of the U.S. National Institutes of Health, or NIH;
- approval of CTAs or INDs for our product candidates to commence clinical trials;
- successful enrollment in, and completion of, preclinical studies and clinical trials;
- successful data from our clinical program that supports an acceptable risk-benefit profile of our product candidates for the intended patient populations;
- receipt of regulatory and marketing approvals from applicable regulatory authorities;

- establishment of arrangements with third-party manufacturers for clinical supply and commercial manufacturing and, where applicable, commercial manufacturing capabilities;
- successful development of our internal manufacturing processes and transfer to larger-scale facilities operated by either a contract manufacturing organization, or CMO, or by us;
- establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates;
- commercial launch of our product candidates, if and when approved, whether alone or in collaboration with others;
- acceptance of the product candidates, if and when approved, by patients, the medical community and third-party payors;
- effective competition with other therapies and treatment options;
- establishment and maintenance of healthcare coverage and adequate reimbursement;
- enforcement and defense of intellectual property rights and claims;
- maintenance of a continued acceptable safety profile of the product candidates following approval; and
- achieving desirable medicinal properties for the intended indications.

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

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

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

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

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

The clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. No products based on gene editing technologies have been approved by regulators. As a result,

the regulatory approval process for product candidates such as ours is uncertain and may be more expensive and take longer than the approval process for product candidates based on other, better known or more extensively studied technologies. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union or how long it will take to commercialize our product candidates. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product candidate to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects may be harmed.

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

The FDA, NIH and the EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates. Within the broader genome product field, uniQure N.V.'s Glybera has received marketing authorization from the European Commission, and to date no gene therapy products have received marketing approval in the United States.

Regulatory requirements in the United States and in other jurisdictions governing gene therapy products have changed frequently and may continue to change in the future. The FDA established the Office of Cellular, Tissue and Gene 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. Prior to submitting an IND, our human clinical trials are subject to review by the NIH Office of Biotechnology Activities, or OBA, Recombinant DNA Advisory Committee, or the RAC. Following an initial review, RAC members make a recommendation as to whether the protocol raises important scientific, safety, medical, ethical or social issues that warrant in-depth discussion at the RAC's quarterly meetings. Even though the FDA decides whether individual gene therapy protocols may proceed under an IND, the RAC's recommendations are shared with the FDA and the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if the FDA has reviewed the trial design and details and has not objected to its initiation or has notified the sponsor that the study may begin. Conversely, the FDA can put an IND on a clinical hold even if the RAC has provided a favorable review or has recommended against an in-depth, public review. Moreover, under guidelines published by the NIH, patient enrollment in our future gene editing clinical trials cannot begin until the investigator for such clinical trial has received a letter from the OBA indicating that the RAC review process has been completed; and Institutional Biosafety Committee, or IBC, approval as well as all other applicable regulatory authorizations have been obtained. In addition to the government regulators, the IBC and institutional review board, or IRB, of each institution at which we conduct clinical trials of our product candidates, or a central IRB if appropriate, would need to review the proposed clinical trial to assess the safety of the trial. In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, the EMA governs the development of gene therapies in the European Union and may issue new guidelines concerning the development and marketing authorization for gene therapy products and require that we comply with these new guidelines.These regulatory review agencies and committees and the new requirements or guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies or trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory agencies and committees and comply with applicable requirements and guidelines. If we fail to do so, we may be required to delay or discontinue development of such product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delays as a result of an increased or lengthier regulatory approval process or further restrictions on the development of our product candidates can be costly and could negatively impact our or our collaborators' ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all.

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

Product candidates we may develop may be associated with undesirable side effects, unexpected characteristics or other serious adverse events, including off-target cuts of DNA, or the introduction of cuts in DNA at locations other than the target sequence. These off-target cuts could lead to disruption of a gene or a genetic regulatory sequence at an unintended site in the DNA, or, in those instances where we also provide a segment of DNA to serve as a repair template, it is possible that following off-target cut events, DNA from such repair template could be integrated into the genome at an unintended site, potentially disrupting another important

gene or genomic element. There also is the potential risk of delayed adverse events following exposure to gene editing therapy due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material. Possible adverse side effects that could occur with treatment with gene editing products include an immunologic reaction after administration which could substantially limit the effectiveness of the treatment. If our CRISPR/Cas9 gene editing technology demonstrates a similar effect, we may decide or be required to halt or delay preclinical development or clinical development of our product candidates. In addition to serious adverse events or side effects caused by any product candidate we may develop, the administration process or related procedures also can cause undesirable side effects. If any such events occur, our clinical trials could be suspended or terminated.

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

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

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

Any of these events could prevent us from achieving or maintaining market acceptance of our CRISPR/Cas9 technology and any product candidates we may identify and develop and could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

Patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- availability and efficacy of approved medications for the disease under investigation;

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

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

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

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

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical and other nonclinical findings made while clinical trials were underway or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events. Moreover, preclinical, non-clinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval.

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

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

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

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

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

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

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

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

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

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

We also may encounter problems hiring and retaining directly or through contract manufacturing organizations the experienced scientific, quality-control and manufacturing personnel needed to operate our manufacturing processes, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements. Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs.

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

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

In particular, gene editing technology is subject to public debate and heightened regulatory scrutiny due to ethical concerns relating to the application of gene editing technology to human embryos or the human germline. For example, in April 2015, Chinese scientists reported on their attempts to edit the genome of human embryos to modify the gene for hemoglobin beta. This is the gene in which a mutation occurs in patients with the inherited blood disorder beta-thalassemia. Although this research was purposefully conducted in embryos that were not viable, the work prompted calls for a moratorium or other types of restrictions on gene editing of human eggs, sperm, and embryos. The Alliance for Regenerative Medicine in Washington, D.C. has called for a voluntary moratorium on the use of gene editing technologies, including CRISPR/Cas9, in research that involves altering human embryos or human germline cells. Similarly, the NIH has announced that it would not fund any use of gene editing technologies in human embryos, noting that there are multiple existing legislative and regulatory prohibitions against such work, including the Dickey-Wicker Amendment, which prohibits the use of appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. Laws in the United Kingdom prohibit genetically modified embryos from being implanted into women, but embryos can be altered in research labs under license from the Human Fertilisation and Embryology Authority. Research on embryos is more tightly controlled in many other European countries.

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

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

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

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

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

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product that we may develop;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

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

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

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising, and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, current Good Manufacturing Practice, or cGMP, requirements relating to quality control, quality assurance and corresponding maintenance of records and documents and requirements regarding recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. The FDA also may place other conditions on approvals including the requirement for a REMS to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the Biologics License Application, or BLA, must submit a proposed REMS before it can obtain approval. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools.

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

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

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

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

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

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

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may also inhibit our ability to commercialize any product candidates we may develop and adversely affect our business, financial condition, results of operations, and prospects.

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

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

- the efficacy, durability and safety of such product candidates as demonstrated in any future clinical trials;
- the potential and perceived advantages of product candidates over alternative treatments;
- the cost of treatment relative to alternative treatments;
- the clinical indications for which the product candidate is approved by FDA or the EMA;
- patient awareness of, and willingness to seek, genotyping;
- the willingness of physicians to prescribe new therapies;
- the willingness of the target patient population to try new therapies;
- the prevalence and severity of any side effects;

- product labeling or product insert requirements of FDA, the EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party payor coverage and reimbursement.

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

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

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

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

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions, some or all of which may have greater access to capital or resources than we do.

We are aware of several companies focused on developing gene editing in various indications using CRISPR/Cas9 gene editing technology, including Intellia Therapeutics, Inc. and Editas Medicine, Inc., or Editas. There can be no certainty that other gene editing technologies will not be considered better or more attractive than our technology for the development of products. For example, Editas has recently exclusively licensed a CRISPR system involving a different protein, Cpf1, which can also edit human DNA as well as advanced forms of CAS9. Editas and certain of its scientific founders have asserted that Cpf1 may work better than Cas9 in some cases. Cas9 may be determined to be less attractive than Cpf1 or other CRISPR proteins that have yet to be discovered.

There are additional companies developing therapies using additional gene editing technologies, including transcription activator-like effector nucleases (TALENs), meganucleases and zinc finger nucleases (ZFNs). These companies include bluebird bio, Cellectis, Poseida Therapeutics, Precision Biosciences, and Sangamo Biosciences. Additional companies developing gene therapy products include Abeona Therapeutics, Avalanche Biotechnologies, Dimension Therapeutics, REGENXBIO, Spark Therapeutics and uniQure.

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

Many of our current or potential competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical studies, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and gene therapy industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with

large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, have broader acceptance and higher rates of reimbursement by third party payors or are less expensive than any products that we may develop or that would render any products that we may develop obsolete or non-competitive. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

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

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

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

The regulations that govern marketing approvals, pricing, and reimbursement for new biologic products vary widely from country to country. In the United States, recently enacted legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some non-U.S. markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval.

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

There may be significant delays in obtaining reimbursement for newly approved products, and reimbursement coverage may be more limited than the purposes for which the product is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any product will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the product and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost products and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently

restrict imports of products from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved products we may develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

Risks Related to Our Relationships with Third Parties

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

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

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

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

Our collaborators or strategic partners may adopt alternative technologies, which could decrease the marketability of our CRISPR/Cas9 gene editing technology. Additionally, because our current 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, 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. 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, our business could be negatively affected. In October 2015, we entered into a four-year collaboration agreement with Vertex to research, develop and commercialize new treatments aimed at the underlying genetic causes of human diseases, including beta-thalassemia and sickle cell. In addition, in December 2015, we entered into an agreement with Bayer Healthcare to create a joint venture to discover and commercialize therapeutics for the treatment of blood disorders, blindness and heart disease in addition to select indications related to other sensory organs, metabolic diseases and autoimmune diseases based on our CRISPR/Cas9 gene editing technology.

We and Bayer Healthcare each hold a 50% interest in the joint venture and each have two designees on the management board. As such, we cannot control all aspects of the clinical development and commercialization of any product candidate developed by the joint venture. Similarly, under our collaboration agreement with Vertex, Vertex has sole authority to select genetic targets to pursue and we will not have control over the development of any product candidates for the selected genetic targets. Our lack of control over the clinical development in our agreements with Bayer Healthcare and Vertex could cause delays or other difficulties in the development and commercialization of product candidates, which may prevent among other things, completion of intended IND filings for the first clinical trial for our hemoglobinopathy program targeting beta-thalassemia in a timely fashion, if at all.

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

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

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

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

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, we have granted exclusive rights to Vertex for certain genetic targets, and during the term of the collaboration agreement, we will be restricted from granting rights to other parties to use our CRISPR/Cas9 technology to pursue therapies that address these genetic targets. Similarly, pursuant to our joint venture agreement with Bayer Healthcare, during the term of the joint venture, and for a specified period after the termination of the joint venture, we will be prohibited from developing products that use our CRISPR/Cas9 technology in specified fields that would compete with the joint venture and Bayer, respectively. The non-competition provisions in each of these agreements could limit our ability to enter into strategic collaborations with future collaborators.

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

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

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

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

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

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

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

We Expect To Rely On Third Parties To Manufacture Our Clinical Product Supplies, And We Intend To Rely On Third Parties For At Least A Portion Of The Manufacturing Process Of Our Product Candidates, If Approved. Our Business Could Be Harmed If The Third Parties Fail To Provide Us With Sufficient Quantities Of Product Inputs Or Fail To Do So At Acceptable Quality Levels Or Prices.

We do not currently own any facility that may be used as our clinical-scale manufacturing and processing facility and must rely on outside vendors to manufacture supplies and process our product candidates in connection with any clinical trial we undertake of such product candidates. We have not yet caused any product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates. We will make changes as we work to optimize the manufacturing process, and we cannot be sure that even minor changes in the process will result in therapies that are safe and effective.

The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA, or other health regulatory agencies in other jurisdictions, pursuant to inspections that will be conducted after we submit an application to the FDA or other health regulatory agencies. We will not control the manufacturing process of, and will be completely dependent on, our contract manufacturing partners for compliance with regulatory requirements, known as cGMP requirements, for manufacture of our product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no direct control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable health regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved.

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

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

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

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order, or recommendation of, any good or service, for which payment may be made under a state or Federal healthcare program, such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Violation of the statute may give rise to criminal and/or civil penalties;
- the federal civil and criminal false claims laws, including the civil False Claims Act, impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval from Medicare, Medicaid, or other government payors that are false, fictitious or fraudulent or knowingly making, using or causing to be made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $5,500 to $11,000 per false claim. In addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false of fraudulent claim for purposes of the False Claims Act;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as further amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations which impose certain requirements on covered entities, including healthcare providers, health plans and healthcare clearing houses, as well as their business associates that perform certain services with respect to safeguarding the privacy, security and transmission of individually identifiable health information that constitutes protected health information, including mandatory contractual terms and restrictions on the use and/or disclosure of such information without appropriate authorization;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing, or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items, or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the federal physician payment transparency requirements, sometimes referred to as the “Sunshine Act” under the Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children’s Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value to physicians and teaching hospitals, and ownership and investment interests held by physicians and other healthcare providers and their immediate family members and applicable group purchasing organizations; and
- analogous laws and regulations in U.S. states, and in other countries, regions or localities in which we may do business, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

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

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

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

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including activities that may be conducted by sales and marketing team we establish, are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal, and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are 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. Rodger Novak, our President and Chief Executive Officer, Dr. Sven Ante (Bill) Lundberg, our Chief Scientific Officer, Dr. Samarth Kulkarni, our Chief Business Officer, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or other employees. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. The loss of the services of our executive officers or other key employees or consultants could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. If we are unable to retain high quality personnel, our ability to pursue our growth strategy will be limited.

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

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

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

- As of December 31, 2016, we had 93 full-time employees and we expect to increase our number of employees and the scope of our operations in 2017 and beyond as we conduct activities as a public company and seek to advance development and if successful, commercialization, of our product candidates. To manage our anticipated development and expansion, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these expansion activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

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

We are exposed to the risk of fraud or other misconduct by our employees, consultants, and commercial partners, and, if we commence clinical trials, our principal investigators. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union and other jurisdictions, provide accurate information to the FDA, the European Commission, and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and in other jurisdications, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations, and prospects, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We contract with third parties for the disposal of these materials and wastes. We will not be able to eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from any use by us of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

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

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

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

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

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

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

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

Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that needs to be re-evaluated frequently. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with generally accepted accounting principles. We have begun the process of documenting, reviewing and improving our internal controls and procedures for compliance with Section 404 of the Sarbanes-Oxley Act of 2002, or SOX, which will require annual management assessment of the effectiveness of our internal control over financial reporting.

Implementing any appropriate changes to our internal controls may distract our officers and employees, entail substantial costs to modify our existing processes and take significant time to complete. These changes may not, however, be effective in maintaining the adequacy of our internal controls, and any failure to maintain that adequacy, or consequent inability to produce accurate financial statements on a timely basis, could increase our operating costs and harm our business. In addition, investors' perceptions that our internal controls are inadequate or that we are unable to produce accurate financial statements on a timely basis may harm our common share price and make it more difficult for us to effectively market and sell our service to new and existing customers.

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.

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; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including floods and fires.

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

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

As we continue to expand our operations, our corporate structure and tax structure has become substantially more complex. In connection with our current and future potential partnerships, we are actively engaged in developing and applying technologies and intellectual property with a view toward commercialization of products globally, often with commercialization partners. In connection with those activities, we already have and will likely continue to engage in complex cross-border and global transactions involving our technology, intellectual property and other assets, between CRISPR and other entities such as partners and licensees, and between companies within the CRISPR group. Such cross-border and global arrangements are both difficult to manage and can potentially give

raise 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 Adequately Protect Our Proprietary Technology Or Obtain And Maintain Patent Protection For The Products We Develop And For Our Technology And Product Candidates, Or If The Scope Of The Patent Protection Obtained Is Not Sufficiently Broad, Our Competitors Could Develop And Commercialize Products And Technology Similar Or Identical To Ours, And Our Ability To Successfully Commercialize Any Product Candidates We May Develop, And Our Technology May Be Adversely Affected.

Our success depends in large part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other countries with respect to our CRISPR/Cas9 platform technology and any proprietary product candidates and technology we develop. Currently, no patents covering our CRISPR/Cas9 platform or product candidates have been issued to us in the United States and one of the patent applications we have licensed that may cover our platform is the subject of an interference proceeding at the United States Patent and Trademark Office, or USPTO, which is discussed below. 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.

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 inventions, obtain, maintain 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.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or product candidates or which effectively prevent others from commercializing competitive technologies and product candidates.

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

to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. 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.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability and our patents may be challenged in the courts or patent offices in the United States and in other jurisdictions. We may be subject to a third party preissuance submission of prior art to the USPTO, or a patent office in another jurisdiction, or become involved in opposition, derivation, revocation, reexamination, post-grant review and inter partes review, or interference proceedings, or litigation challenging our patent rights or the patent rights of others. Indeed, certain of our fundamental intellectual property has been subject to third party observations outside the United States and interference proceedings within the United States. Competitors may 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 patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

We Are Required To Pay Royalties Under Our License Agreements With Third-Party Licensors, And We Must Use Commercially Reasonable Diligence Efforts And Meet Milestones To Maintain Our License Rights.

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

Some Of Our In-licensed Patent Applications Are Subject To Priority Disputes And Inventorship Disputes, Including An Active Interference Proceeding With The Broad Institute, Massachusetts Institute of Technology, President And Fellows of Harvard College, In Front Of The United States Patent And Trademark Office. In Addition, Our Owned And In-Licensed Patents And Other Intellectual Property May Be Subject To Further Priority Disputes Or To Inventorship Disputes And Similar Proceedings. If We Or Our Licensors Are Unsuccessful In Any Of These Proceedings, We May Be Required To Obtain Licenses From Third Parties, Which May Not Be Available On Commercially Reasonable Terms Or At All, Or To Cease The Development, Manufacture, And Commercialization Of One Or More Of The Product Candidates We May Develop, Which Could Have A Material Adverse Impact On Our Business.

In January 2016, at our request, the USPTO declared an interference between one of the pending U.S. patent applications we licensed from Dr. Charpentier and twelve issued U.S. patents, and subsequently added one U.S. patent application, owned jointly by the Broad Institute and Massachusetts Institute of Technology and, in some instances, the President and Fellows of Harvard College, collectively referred to as 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 both of these parties. There are currently two parties to this interference. Because our application was filed first, the USPTO designated Dr. Charpentier, the Regents of the University of California, or California, and the University of Vienna, or Vienna, collectively as “Senior Party” and designated Broad

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

Furthermore, we may be involved in other interference proceedings or other disputes in the future. 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 currently 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, Rockefeller University has filed a continuation application (U.S. Serial No. 14/324,960) of an application filed by the Broad, but which names Rockefeller's employee Luciano Marraffini as co-inventor of CRISPR/Cas9 technology; Vilnius University has filed applications in the United States and in other jurisdictions (published internationally as WO2013/141680 and WO2013/142578), Harvard University has filed applications in the United States and in other jurisdictions (published internationally as WO2014/099744), and Sigma-Aldrich has filed applications in the United States and in other jurisdictions (published internationally as WO2014/089290), each claiming aspects of CRISPR/Cas9 technology based on applications claiming priority to provisional filings in 2012. Numerous other filings are based on provisional applications filed after 2012.

Broad, Toolgen, Vilnius and other parties routinely file international counterparts of their U.S. applications, some of which have been granted or could in future be granted in Europe and/or other non-U.S. jurisdictions. We and third parties have initiated opposition proceedings against some of these grants, and we may in the future oppose other grants to these or other applicants. Similarly, our intellectual property may in the future become involved in opposition proceedings in Europe or other jurisdictions.

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 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 the interference proceedings with Broad, 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 family of patent applications we have in-licensed from Dr. Charpentier is the foundational patent protection for our core gene editing technology. However, that family includes other named inventors who assigned their rights either to California or to Vienna. As such, the intellectual property 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 Biosciences, Inc. and Caribou's licensee Intellia Therapeutics, Inc. 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 CRISPR/Cas9 intellectual property, 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 our foundational intellectual property from a third party, and we expect to continue to in-license additional third-party intellectual property rights as we expand our CRISPR/Cas9 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 CRISPR/Cas9 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 CRISPR/Cas9 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 CRISPR/Cas9 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 filed in Europe, 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 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 CRISPR/Cas9 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, in addition to the ongoing interference 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, including parties involved in ongoing interference proceedings, 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 patents involved in the interference proceeding described above that may be asserted to encompass our CRISPR/Cas9 technology. 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 third parties could potentially assert infringement claims against us, which 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 the invention was 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's 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, scheduled to begin in 2017, 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.

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 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:

- 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.

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 after 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 will need to devote a substantial amount of time towards maintaining compliance with these requirements. Moreover, these requirements will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, the rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our board of directors. We are currently evaluating these rules and regulations and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

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. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with SOX Section 404 within the prescribed period, we are engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. 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 stock price has been and in the future may be subject to substantial volatility. For example, our stock traded within a range of a high price of $25.00 and a low price of $11.63 per share for the period October 19, 2016, our first day of trading on The NASDAQ Global Market, through March 1, 2017. As a result of this volatility, our shareholders could incur substantial losses. In addition, the market price for our common stock 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 agreement;
- 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.

In recent years, the stock market in general, and the market for pharmaceutical and biotechnology companies in particular, has experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to changes in the operating performance of the companies whose stock is experiencing those price and volume fluctuations. Broad market and industry factors may seriously affect the market price of our common shares, regardless of our actual operating performance. Following periods of such volatility in the market price of a company’s securities, securities class action litigation has often been brought against that company. Because of the potential volatility of our common share price, we may become the target of securities litigation in the future. Securities litigation could result in substantial costs and divert management’s attention and resources from our business.

If 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.

A Significant Portion Of Our Total Outstanding Common Shares May Be Sold Into The Market In The Near Future, Which Could Cause The Market Price Of Our Common Shares To Decline Significantly, Even If Our Business Is Doing Well.

Sales of a substantial number of our common shares in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of common shares intend to sell shares, could reduce the market price of our common stock.

All lock-up agreements entered into in connection with our initial public offering are expected to expire on April 17, 2017. Following the lockup expiration, outstanding common shares may be freely sold in the public market at any time to the extent permitted by Rules 144 and 701 under the Securities Act of 1933, as amended (the "Securities Act"), or to the extent that such shares have already been registered under the Securities Act and are held by non-affiliates of ours.

Moreover, holders of a substantial number of our common shares have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We also have registered substantially all common shares that we may issue under our equity compensation plans or that are issuable upon exercise of outstanding options. These common shares can be freely sold in the public market upon issuance and once vested, subject to volume limitations applicable to affiliates. If any of these additional common shares are sold, or if it is perceived that they will be sold, in the public market, the market price of our common shares could decline.

Our Executive Officers, Directors, And Principal Stockholders, If They Choose To Act Together, Have The Ability To Control All Matters Submitted To Stockholders For Approval.

As of March 1, 2017, common shares beneficially owned by our executive officers, directors and principal shareholders, including Vertex, Bayer Healthcare and other shareholders and their affiliates who owned more than 5% of our outstanding common shares totaled 31,822,899. As a result, these shareholders, if they were to act together, would be able to influence our management and affairs and all matters requiring shareholder approval, including the election of directors and approval of significant corporate transactions. This concentration of ownership may have the effect of delaying or preventing a change in control of our company and might affect the market price of our common shares.

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.

We Are An "Emerging Growth Company," And The Reduced Disclosure Requirements Applicable To Emerging Growth Companies May Make Our Common Shares Less Attractive To Investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earlier of (i) the last day of the fiscal year in which we have total annual gross revenue of $1 billion or more; (ii) December 31, 2021, being the last day of the fiscal year following the fifth anniversary of the date of the completion of the IPO; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission, which means the market value of our common shares that is held by non-affiliates exceeds $700 million as of the prior June 30th. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of SOX;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- being permitted to present only two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure in this prospectus;

- reduced disclosure obligations regarding executive compensation; and
- the "say on pay" provisions (requiring a non-binding shareholder vote to approve compensation of certain executive officers) the "say on golden parachute" provisions (requiring a non-binding shareholder vote to approve golden parachute arrangements for certain executive officers in connection with mergers and certain other business combinations) of the Dodd-Frank Wall Street Reform and Protection Act, or Dodd-Frank Act, and some of the disclosure requirements of the Dodd-Frank Act relating to compensation of our chief executive officer.

We may choose to take advantage of some, but not all, of the available exemptions. We cannot predict whether investors will find our common shares less attractive if we rely on these exemptions. If some investors find our common shares less attractive as a result, there may be a less active trading market for our common shares and our common share price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

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

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

We are a Swiss corporation. Our business and 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 Basel, 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 Basel, Switzerland.

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

We are a Swiss corporation subject to the laws of Switzerland. 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. Any future changes or differences in corporate law principles could adversely affect the rights of U.S. investors.

Our Status As A Swiss Corporation Means That Our Shareholders Enjoy Certain Rights That May Limit Our Flexibility To Raise Capital, Issue Dividends And Otherwise Manage Ongoing Capital Needs And May Cause Us To Be Unable To Make Distributions Without Subjecting Our Shareholders To Swiss Withholding Tax.

Swiss law 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 cancellation of treasury shares must be approved by shareholders. Swiss law also requires that our shareholders themselves resolve to, or authorize our board of directors to, increase our share capital. While our shareholders may authorize share capital that can be issued by our board of directors without additional shareholder approval, Swiss law limits this authorization to 50% of the issued share capital at the time of the authorization. The authorization, furthermore, has a limited duration of up to two years and must be renewed by the shareholders from time to time thereafter in order to be available for raising capital. Additionally, subject to specified exceptions, including exceptions explicitly described in our articles of association, Swiss law grants pre-emptive rights to existing shareholders to subscribe for new issuances of shares. Swiss law also does not provide as much flexibility in the various rights and regulations that can attach to different categories of shares as do the laws of some other jurisdictions, such as in the United States. These Swiss law requirements relating to our capital management may limit our flexibility, and situations may arise where greater flexibility would have provided benefits to our shareholders.

Under Swiss law, we, as a Swiss corporation, may pay dividends only if we have sufficient distributable profits from previous fiscal years, or if we have distributable reserves, each as evidenced by its audited statutory balance sheet, and after allocations to reserves required by Swiss law and our articles of association have been deducted. Freely distributable reserves are generally booked either as "free reserves" or as "capital contributions" (*Kapitaleinlagen*, contributions received from shareholders) in the "reserve from capital contributions." Distributions may be made out of registered share capital—the aggregate nominal value of our registered share capital—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. While we would also be able to pay dividends out of distributable profits or freely distributable reserves, if any, such dividends would be subject to Swiss withholding taxes. There can be no assurance that we will have sufficient distributable profits, free reserves, reserves from capital contributions or registered share capital to pay a dividend or effect a capital reduction, that our shareholders will approve dividends or capital reductions proposed by us or that we will be able to meet the other legal requirements for dividend payments or distributions as a result of capital reductions.

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

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

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

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

During our 2016 taxable year we believe that we had certain shareholders that were Ten Percent Shareholders for United States federal income tax purposes. However, our CFC status for the taxable year ended December 31, 2016 and our current taxable year is uncertain and we may be a CFC for the taxable year ended December 31, 2016, our current taxable year or a following year. U.S. holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a PFIC, we generally will not be treated as a PFIC with respect to those U.S. holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Certain U.S. Shareholders May Be Subject to Adverse Tax Consequences If We Are 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 the IPO 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 2016 taxable year, we intend to provide the information that is necessary for you to make a QEF election with respect to us for the 2016 taxable year. We intend to provide such information on our website (www.crisprtx.com). However, we have not determined whether any of our subsidiaries are lower-tier PFICs and we do not intend to make the necessary information available to you with respect to any lower-tier PFICs. You are urged to consult your own tax advisors regarding the availability, and advisability, of, and procedure for making, a QEF election, including, with respect to any lower-tier PFICs.

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 a Swiss corporation organized under the laws of Switzerland and our registered office and domicile is located in Basel, 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 our directors and officers residing outside the United States. Additionally, even though we have appointed CT Systems Corp. as our agent to effect service of process upon us in the United States, investors may be unable to enforce against us or our directors and officers residing outside the United States 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 Basel, Switzerland, where we occupy approximately 365 square feet of office space on a month-to month lease. We also have facilities in Cambridge, Massachusetts, where we occupy approximately 65,376 square feet of laboratory and office space under a sublease that expires in December 2026. We also lease approximately 19,817 square feet of additional office and laboratory space in Cambridge, Massachusetts pursuant to a lease that expires in February 2022. In London, England, we occupy and maintain approximately 350 square feet of office space pursuant to a real estate license agreement with a term that renews every six months. 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 United States Patent and Trademark Office, or USPTO, declared an interference between one of the pending U.S. patent applications we have in-licensed from Dr. Charpentier and twelve issued U.S. patents and one U.S. patent application owned jointly by The Broad Institute, Massachusetts Institute of Technology, President and Fellows of Harvard College, or Broad. The interference was redeclared in March 2016 to add a U.S. patent application owned by Broad. An interference is a proceeding conducted at the USPTO by the Patent Trial and Appeal Board, or PTAB, to determine which party was first to invent subject matter by at least two parties. There are currently two parties to this interference. Our in-licensed patent application is co-owned among Dr. Charpentier, the Regents of the University of California, and the University of Vienna, whom the USPTO designated collectively as "Senior Party"; Broad was designated as "Junior Party." 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 particular, the Junior Party's claims in the interference were all limited to uses in eukaryotic cells, while the Senior Party's claims in the interference were not limited to uses in eukaryotic cells but included uses in all settings. Either party can appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In parallel, either party can also pursue existing or new patent applications in the U.S. and elsewhere. Going forward, either party as well as other parties could seek a new interference related to the uses of the technology in eukaryotic cells or other aspects of the technology, and any existing or new patents could be the subject of other challenges to their validity of enforceability. In the context of a second interference or in other proceedings, a determination could be reached regarding that the Senior Party was not the first to invent, or it could be concluded that the contested subject matter is not patentable to the Senior Party and is patentable to the Junior Party, which in this case could preclude our U.S. patent applications from issuing as patents, in which case the proceedings would result in our losing the right to

protect core innovations and our freedom to practice our core gene editing technology. If there is a second interference, either party could again appeal an adverse decision to the U.S. Court of Appeals for the Federal Circuit. In any case, it may be years before there is a final determination on priority. In addition, both the Broad and Toolgen Inc. have filed international counterparts of their U.S. applications, some of which were granted in Europe and/or other jurisdictions, and Vilnius University and other third parties also have international counterparts of U.S. patent applications that could proceed to grant. 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, if we should obtain patent grants in the U.S., Europe and other jurisdictions, these could also be the subject of oppositions or other post-grant procedures sought by third parties in order to revoke the grants or narrow the scope of granted claims. Going forward, with existing and new challenges being filed against CRISPR/Cas9 cases in the U.S., Europe and elsewhere, and considering the number of interested parties, it is reasonable to expect that patents directed to the underlying technology will continue to be the subject of ongoing disputes over at least the next several years, and potentially beyond as decisions in favor or against particular parties may be the subject of appeals.

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

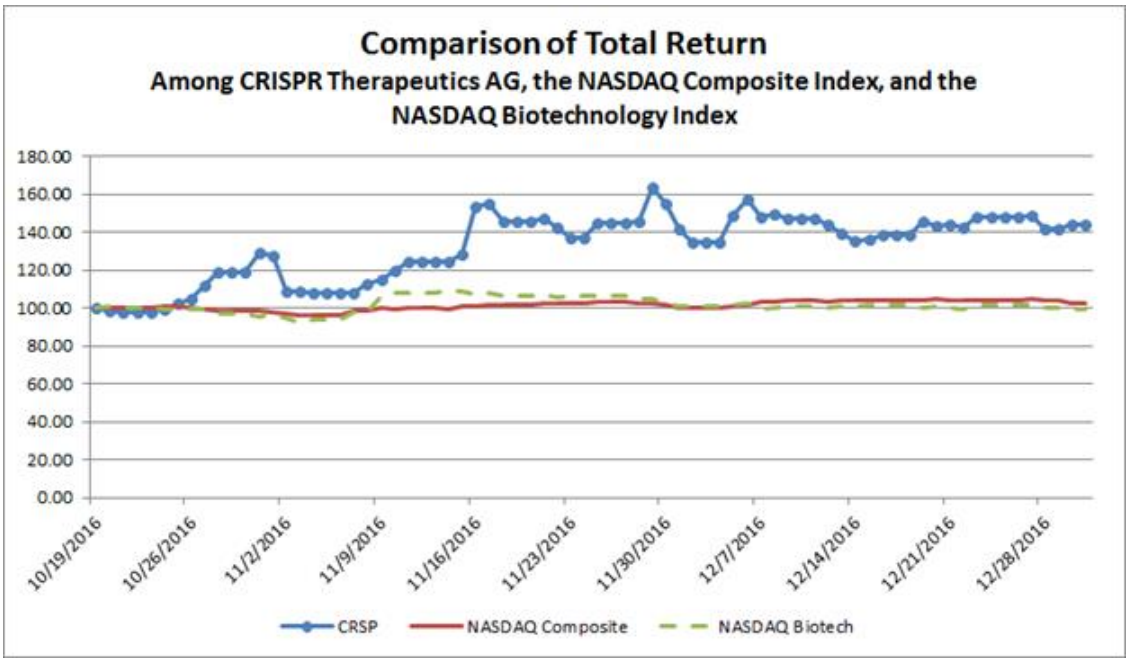
Our common shares trade on the NASDAQ Global Market under the symbol "CRSP" since our initial public offering on October 18, 2016. Prior to this time, there was no public market for our common shares. As a result, the following table shows the high and low sale prices per share of our common shares as reported on the Nasdaq Global Market for the period indicated:

	Market Price	
	High	Low
Fourth Quarter (beginning October 19, 2016)	$ 23.97	$ 13.75

Stock Performance Graph

The graph set forth below compares the cumulative total stockholder return on our common stock between October 18, 2016 (the date of our initial public offering) and December 31, 2016, 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 18, 2016 in our common stock, the Nasdaq Biotechnology Index and the Nasdaq Composite Index and assumes the reinvestment of dividends, if any. The graph assumes our closing sales price on October 19, 2016 of $14.09 per share as the initial value of our common shares and not the initial offering price to the public of $14.00 per share.

The comparisons shown in the graph below are based upon historical data. We caution that the stock price performance shown in the graph below is not necessarily indicative of, nor is it intended to forecast, the potential future performance of our common shares. Information used in the graph was obtained from the Nasdaq Stock Market LLC, a financial data provider and a source believed to be reliable. The Nasdaq Stock Market LLC is not responsible for any errors or omissions in such information.



Holders

As of March 1, 2017, we had approximately 49 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.

Use of Proceeds from Registered Securities

On October 24, 2016, we closed the sale of 4,429,311 of our common shares in our initial public offering, or the IPO, inclusive of 429,311 common shares sold by us pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the offering, at a price to the public of $14.00 per share. The aggregate net proceeds received by us from the offering were $53.7 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. None of these expenses consisted of payments made by us to directors, officers or persons owning 10% or more of our common shares or to their associates, or to our affiliates. Concurrent with the IPO, we issued and sold 2,500,000 common shares to Bayer BV, at the IPO price $14.00 per share, or (the "Concurrent Private Placement"), resulting in aggregate net proceeds of $35.0 million in accordance with the terms of our subscription agreement with Bayer BV.

The offer and sale of the shares in the IPO was registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 333-213577), which was filed with the SEC, on September 9, 2016 and amended subsequently and declared effective on October 18, 2016. Citigroup Global Markets Inc., Piper Jaffray & Co. and Barclays Capital Inc. acted as joint book-running managers of the offering.

There has been no material change in the planned use of proceeds from our IPO as described in our final prospectus filed with the SEC on October 19, 2016 pursuant to Rule 424. We invested the unused proceeds from the offering in cash equivalents in accordance with our investment policy.

Purchase of Equity Securities

There were no repurchases of our common shares made during the year ended December 31, 2016. During 2016, Fay Corporation transferred 274,184 shares to us which are reflected as treasury shares on the consolidated balance sheet as of December 31, 2016. Common shares totaling 170,689, which represents the balance of the 600,000 shares granted to the underwriters pursuant to the overallotment option that were not sold in the IPO, were transferred to the Company and are reflected as treasury shares on the consolidated balance sheet as of December 31, 2016.

Item 6. Selected Financial Data.

SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations", the consolidated financial statements and related notes, and other financial information included in this Annual Report on Form 10-K.

The consolidated statements of operations data for the years ended December 31, 2016, 2015, and 2014 and the consolidated balance sheet data as of December 31, 2016 and 2015 are derived from our audited consolidated financial statements included in this Annual Report on Form 10-K. Historical results are not necessarily indicative of the results to be expected in future periods.

	Years Ended December 31,		
	2016	2015	2014
	(in thousands, except share and per share amounts)		
Consolidated Statements of Operations Data:			
Collaboration revenue	$ 5,164	$ 247	$ —
Operating expenses:			
Research and development	42,238	12,573	1,513
General and administrative	31,056	13,403	5,114
Total operating expenses	73,294	25,976	6,627
Loss from operations	(68,130)	(25,729)	(6,627)
Other income (expense), net	45,412	(92)	(236)
Net loss before (provision for) benefit from income taxes	(22,718)	(25,821)	(6,863)
(Provision for) benefit from income taxes	(484)	(7)	63
Net loss	(23,202)	(25,828)	(6,800)
Foreign currency translation adjustment	(18)	(6)	(2)
Comprehensive loss	$ (23,220)	$ (25,834)	$ (6,802)
Reconciliation of net loss to net loss attributable to common shareholders:			
Net loss	$ (23,202)	$ (25,828)	$ (6,800)
Loss attributable to noncontrolling interest	25	325	536
Loss on extinguishment of redeemable convertible preferred shares	—	—	(745)
Net loss attributable to common shareholders	$ (23,177)	$ (25,503)	$ (7,009)
Net loss per share attributable to common shareholders, basic and diluted	$ (1.89)	$ (5.06)	$ (1.97)
Weighted-average common shares outstanding, basic and diluted	12,257,483	5,037,404	3,559,985

	December 31,	
	2016	2015
	(in thousands)	
Consolidated Balance Sheet Data:		
Cash	$ 315,520	$ 155,961
Working capital	298,190	146,685
Total assets	344,962	159,423
Redeemable convertible preferred shares	—	64,521
Total shareholders' deficit	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 the disease. We believe that our scientific expertise, together with our approach, may enable an entirely new class of highly active and potentially curative treatments for patients for whom current biopharmaceutical approaches have had limited success.

Since our inception in October 2013, we have devoted substantially all of our resources to initiating the conduct of our research and development efforts, identifying potential product candidates, undertaking drug discovery and preclinical development activities, building and protecting our intellectual property portfolio, 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, convertible loans and collaboration agreements with strategic partners. From our inception through December 31, 2016, we raised an aggregate of $308.4 million, of which $125.2 million consisted of gross proceeds from private placements of our preferred shares, $73.2 million from the issuance of convertible loans, $75.0 million from an upfront payment under our collaboration with Vertex Pharmaceuticals, Incorporated, or Vertex, and $35.0 million from a technology access fee related to our license of technology to Casebia Therapeutics, LLP, our joint venture with Bayer HealthCare LLC, or Bayer HealthCare.

In October 2016, we issued and sold 4,429,311 of our common shares, including 429,311 common shares sold pursuant to the underwriters' partial exercise of their option to purchase additional common shares, in our initial public offering, or the IPO, at a public offering price of $14.00 per share, for aggregate gross proceeds of approximately $62.0 million. Concurrent with the IPO, we issued and sold an aggregate of 2,500,000 common shares to Bayer Global Investments BV, or Bayer BV, in a private placement, at the IPO price of $14.00 a share, for aggregate net proceeds of $35.0 million.

All of our revenue to date has been collaboration revenue. We have incurred significant net operating losses in every year since our inception and expect to continue to incur net operating losses for the foreseeable future. As of December 31, 2016, we had $315.5 million in cash and an accumulated deficit of $57.1 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 portfolio, further develop our gene editing platform; hire additional research, clinical and scientific personnel; and incur additional costs associated with operating as a public company.

Collaboration Agreement and Joint Venture Agreement

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

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

In connection with the JV Agreement, the JV was required to pay us an aggregate amount of $35.0 million technology access fee, consisting of an upfront payment of $20.0 million, which was paid at the closing of the JV Agreement in March 2016, and another payment of $15.0 million for specified intellectual property rights relating to our CRISPR/Cas9 technology outside of the United States, which was paid in December 2016. In January 2016, we also issued a convertible loan to Bayer BV (the "Bayer Convertible Loan") for gross proceeds of $35.0 million which was immediately converted to Series B Preferred Shares at a conversion price of $13.43 per share. Concurrent with the IPO in October 2016, we issued and sold 2,500,000 common shares to Bayer BV, at the IPO price of $14.00 per share resulting in aggregate net proceeds of $35.0 million.

Financial Overview

Revenue

We have not generated any revenue to date from product sales and do not expect to do so in the near future. During the year ended December 31, 2016, and 2015, we recognized $5.2 million and $0.2 million, respectively, of revenue related to our collaboration agreements with Vertex and Casebia. As of December 31, 2016, we had not received any milestone or royalty payments under the Vertex collaboration agreement. For additional information about our revenue recognition policy, see the "Critical Accounting Policies and Estimates—*Revenue*."

Research and Development Expenses

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

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

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

- successful completion of preclinical studies and Investigational New Drug-enabling studies;
- successful enrollment in, and completion of, clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity;
- launching commercial sales of the product, if and when approved, whether alone or in collaboration with others;
- acceptance of the product, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies and treatment options;
- a continued acceptable safety profile following approval;
- enforcing and defending intellectual property and proprietary rights and claims; and
- achieving desirable medicinal properties for the intended indications.

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

Except for activities we perform in connection with our collaborations with Vertex and Casebia, we do not track research and development costs on a program-by-program basis. We plan to track research and development costs for individual development programs when we identify a product candidate from the program that we believe we can advance into clinical trials.

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

General and Administrative Expenses

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

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

Results of Operations

Comparison of Years Ended December 31, 2016, and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015, together with the dollar change in those items:

	Year Ended December 31,		Period-to-Period Change
	2016	2015	
	(in thousands)		
Collaboration revenue	$ 5,164	$ 247	$ 4,917
Operating expenses:			
Research and development	42,238	12,573	29,665
General and administrative	31,056	13,403	17,653
Total operating expenses	73,294	25,976	47,318
Loss from operations	(68,130)	(25,729)	(42,401)
Other income (expense), net	45,412	(92)	45,504
Net loss before (provision for) benefit from income taxes	(22,718)	(25,821)	3,103
(Provision for) benefit from income taxes	(484)	(7)	(477)
Net loss	$ (23,202)	$ (25,828)	$ 2,626

Collaboration Revenue

Collaboration revenue for the year ended December 31, 2016 was $5.2 million, compared to $0.2 million for the year ended December 31, 2015. The increase of $5.0 million was primarily due to a full year's worth of research and development service revenue from the collaboration with Vertex of $4.0 million, and research and development service revenue of $1.2 million under a collaboration agreement with Casebia. During the year ended December 31, 2015, we recognized $0.2 million of research and development service revenue related to the collaboration with Vertex.

Research and Development Expenses

Research and development expenses for the year ended December 31, 2016 was $42.2 million, compared to $12.6 million for the year ended December 31, 2015. The increase of $29.7 million in research and development expenses was primarily attributable to approximately $10.6 million in increased facilities costs including rent and utilities, $9.0 million in increased research and development variable process and platform development costs, $10.4 million in increased research and development employee compensation costs, partially offset by a $0.4 million reduction of license fees and consulting expenses.

General and Administrative Expenses

General and administrative expenses were $31.1 million for the year ended December 31, 2016, compared to $13.4 million for the year ended December 31, 2015. The increase of $17.7 million was primarily due to the following increases in expenses: $8.5 million of employee-related costs to support our overall growth; $3.9 million of intellectual property costs including third-party costs to procure the issuance of patents in jurisdictions outside the United States and costs related to an interference proceeding with respect to our in-licensed intellectual property, $2.0 million in non-recurring shareholder PFIC settlements, $1.1 million in facilities costs including rent and utilities, $1.6 million in capital and franchise taxes related to financing rounds, and $0.5 million of professional and consulting fees to support the requirements of being a public company.

Other Income (Expense), Net

Other income (expense), net, was $45.4 million of income for the year ended December 31, 2016, compared to $0.1 million of expense for the year ended December 31, 2015. The increase of $45.5 million was primarily due to a $78.6 million gain recognized in connection with the formation of Casebia which equaled the value of cash consideration received from Casebia and the fair value of the Company's equity interest in Casebia as of the formation of the JV, combined with an $11.5 million gain recognized on extinguishment of convertible loans with Vertex, all of which was partially offset by $36.5 million in 2016 equity method losses, and $8.1 million of interest expense related to a convertible loan with Bayer.

Comparison of Years Ended December 31, 2015, and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014, together with the dollar change in those items:

	Year Ended December 31,		Period-to-Period Change
	2015	2014	
	(in thousands)		
Collaboration revenue	$ 247	—	$ 247
Operating expenses:			
Research and development	12,573	1,513	11,060
General and administrative	13,403	5,114	8,289
Total operating expenses	25,976	6,627	19,349
Loss from operations	(25,729)	(6,627)	(19,102)
Other expense, net	(92)	(236)	144
Net loss before (provision for) benefit from income taxes	(25,821)	(6,863)	(18,958)
(Provision for) benefit from income taxes	(7)	63	(70)
Net loss	$ (25,828)	$ (6,800)	$ (19,028)

Collaboration Revenue

We recognized collaboration revenue during the year ended December 31, 2015 of $0.2 million, related to our collaboration agreement with Vertex. We did not record any revenue during the year ended December 31, 2014.

Research and Development Expenses

Research and development expenses increased by $11.1 million to $12.6 million for the year ended December 31, 2015, from $1.5 million for the year ended December 31, 2014. The increase in research and development expenses was primarily attributable to an increase in employee costs of $4.8 million associated with salaries, benefits and equity-based compensation expenses from hiring additional personnel, an increase in professional service expense of $2.0 million, an increase in facilities expense of $2.3 million, principally associated with the establishment in February 2015 of our research and development center in Cambridge, Massachusetts, and an increase in licensing fees and related payments of $1.4 million.

General and Administrative Expenses

General and administrative expenses increased by $8.3 million to $13.4 million for the year ended December 31, 2015, from $5.1 million for the year ended December 31, 2014. The increase in general and administrative expenses was primarily attributable to increase in employee costs of $1.9 million associated with salaries, benefits and equity-based compensation expenses from hiring additional senior personnel, increased consulting and professional fees of $3.2 million, including directors' fees, audit and accounting fees, and consultant fees; and increased intellectual property costs of $1.9 million, including third-party costs to procure the issuance of patents in jurisdictions outside the United States and costs related to the ongoing interference proceedings with respect to our in-licensed intellectual property.

Other Expense, Net

Other expense, net decreased by $0.1 million for the year ended December 31, 2015 due to a decrease in the loss on foreign currency remeasurement of $0.2 million, offset by an increase in non-cash interest expense related to the convertible loans of $0.1 million.

Liquidity and Capital Resources

From our inception through December 31, 2016, we raised an aggregate of $308.4 million, of which $125.2 million consisted of gross proceeds from private placements of preferred shares, $73.2 million from the issuance of convertible loans, an up-front payment under our collaboration agreement with Vertex of $75.0 million, and a technology access fee of $35.0 million from Casebia, pursuant to our JV Agreement with Bayer HealthCare.

On October 24, 2016, we completed our IPO whereby we sold 4,429,311 common shares, inclusive of 429,311 common shares sold by us pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the offering, at a price to the public of $14.00 per share. The aggregate net proceeds received by us from the offering were $53.7 million, after deducting underwriting discounts and commissions and other offering expenses payable by us. Concurrent with the IPO, we issued and sold 2,500,000 common shares to Bayer BV, at the IPO price $14.00 per share, or the Concurrent Private Placement, resulting in aggregate net proceeds of $35.0 million in accordance with the terms of our subscription agreement with Bayer BV.

As of December 31, 2016, we had $315.5 million in cash, of which approximately $309.8 million was held outside of the United States.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, research and development activities, compensation and related expenses, laboratory and related supplies, legal and other regulatory expenses, patent prosecution filing and maintenance costs for our licensed intellectual property and general overhead costs. We expect our expenses to increase compared to prior periods in connection with our ongoing activities, particularly as we continue research and development and preclinical activities, initiate preclinical studies to support initial drug applications, and as we begin in 2017 to occupy our new office and laboratory facility. In addition, we expect to incur additional costs associated with operating as a public company.

Because our research programs are still in preclinical development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts necessary to successfully complete the development and commercialization of any future product candidates or whether, or when, we may achieve profitability. Until such time as we can generate substantial product revenues, if ever, we expect to finance our cash needs through a combination of equity or debt financings and collaboration arrangements. We are entitled to research payments under our collaboration with Vertex. Additionally, we are eligible to earn payments, in each case, on a per-product basis under the JV Agreement and our collaboration with Vertex and Casebia. Except for these sources of funding, we do not have any committed external source of liquidity. To the extent that we raise additional capital through the future sale of equity or debt securities, the ownership interest 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 that the net proceeds from our IPO, including the proceeds from the Concurrent Private Placement with Bayer BV, together with our existing cash, will enable us to fund our operating expenses and capital expenditures for at least the next 24 months, without giving effect to any additional proceeds we may receive under our collaboration agreement with Vertex and the JV. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect.

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

Sources of Liquidity

Cash Flows

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

	Year Ended December 31,		
	2016	2015	2014
	(in thousands)		
Net cash (used in) provided by operating activities	$ (55,310)	$ 59,428	$ (4,793)
Net cash provided by (used in) investing activities	31,884	(1,154)	—
Net cash provided by financing activities	183,220	96,733	5,123
Effect of exchange rate changes on cash	(235)	9	254
Net increase in cash and cash equivalents	$ 159,559	$ 155,016	$ 584

Net Cash (Used in) Provided by Operating Activities

Net cash used in operating activities was $55.3 million for the year ended December 31, 2016 and primarily consisted of a net loss of $23.2 million adjusted for non-cash items (including equity-based compensation expense of $10.8 million, non-cash interest expense of $8.1 million, depreciation and amortization expense of $0.9 million, loss from equity method investment of $36.4 million, other income of $78.6 million recognized in connection with the formation of our JV with Bayer HealthCare, and a gain on extinguishment of the Vertex convertible loan of $11.5 million), an increase in prepaid expenses and other current assets of $1.1 million, and an increase in accounts receivable of $2.8 million, and an increase in restricted cash of $2.5 million, partially offset by an increase in accounts payable and accrued expenses of $3.9 million, deferred revenue of $1.9 million, and deferred rent of $2.4 million.

The net cash provided by operating activities was $59.4 million for the year ended December 31, 2015, and consisted primarily of a net loss of $25.8 million adjusted for non-cash items (including equity-based compensation expense of $3.7 million), depreciation of $0.1 million, along with an increase in prepaid expenses and other assets of $1.0 million and an increase of restricted cash of $0.7 million, offset by an increase in accounts payable and accrued expenses of $7.7 million, deferred revenue of $75.1 million, and deferred rent of $0.2 million.

Net cash used in operating activities was $4.8 million for the year ended December 31, 2014 and consisted primarily of a net loss of $6.8 million adjusted for non-cash items (including equity-based compensation expense of $0.7 million, amortization expense of $38 thousand and foreign currency remeasurement loss of $0.3 million), along with an increase in accounts payable and accrued expenses of $1.6 million

Net Cash Provided by (Used in) Investing Activities

Net cash provided by investing activities for the year ended December 31, 2016 was $31.9 million and consisted primarily of consisted of proceeds of $35.0 million from our contribution of intellectual property to the JV, offset by our contributions to the JV of $0.1 million, and the purchase of property and equipment of $3.0 million primarily associated with the commencement of internal research and development. We expect purchases of property and equipment to continue to increase in each of 2017 and 2018 as we build-out and outfit the office and laboratory space we began to occupy in December 2016.

Net cash used in investing activities was $1.2 million during the year ended December 31, 2015, compared to $0 during the year ended December 31, 2014, which resulted solely from the purchase of property and equipment primarily associated with the commencement of internal research and development operations in Cambridge, Massachusetts.

Net Cash Provided by Financing Activities

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

Net cash provided by financing activities was $96.7 million for the year ended December 31, 2015, compared to $5.1 million for the year ended December 31, 2014. The cash provided by financing activities for the year ended December 31, 2015 primarily consisted of net proceeds of $5.3 million related to a subscription receivable for Series A-2 Preferred Shares, $22.9 million from the issuance of Series A-3 Preferred Shares, $30.5 million from the issuance of Series B Preferred Shares and $38.2 million from the issuance of a convertible loan with Vertex and certain existing shareholders. The cash provided by financing activities for the year ended December 31, 2014 primarily consisted of net proceeds of $5.1 million from the issuance of Series A-2 Preferred Shares.

Contractual Obligations

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2016 (in thousands):

	Year 1	Year 2-3	More than 3 Years	Total
Operating lease and sublease commitments (1) (2)	$ 6,685	$ 13,055	$ 44,185	$ 63,925

(1) We lease additional office and laboratory space in Cambridge, Massachusetts under a non-cancelable operating lease that expires in February 2022, with one optional five- year extension period. We also lease office facilities in London, England that expires in July 2017 and is subject to a six month renewal, and corporate housing in Cambridge, Massachusetts which expires in November 2017 subject to a one year renewal.

(2) In May 2016, we entered into an agreement to sublease primary office and laboratory space in Cambridge, Massachusetts, for an initial term of ten years with an option to extend the lease for an additional five years. We have the option to extend the term of the sublease by five years if the sublessor does not desire to utilize the space for itself or its affiliates at the time of expiration of the initial term. The sublease contains escalating rent clauses which require higher rent payments in future years. We recognize rent expense on a straight-line basis over the term of the lease, including any rent-free periods.

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

We have engaged several research institutions to identify new delivery strategies and applications of the CRISPR/Cas9 technology. As a result of these efforts, we sponsored five research programs during 2016. We have committed spending in three of these programs through 2018.

We have long-term liabilities associated with uncertain tax positions recorded under ASC 740, *Income Taxes* totaling $0.2 million. Due to the complexity associated with tax uncertainties, we cannot reasonably make a reliable estimate of the period in which we expect to settle these non-current liabilities. See Note 14 to our consolidated financial statements contained in Item 15 of this Annual Report for more information on our unrecognized tax benefits.

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

Off-Balance Sheet Arrangements

As of December 31, 2016, we do not have any off-balance sheet arrangements, as defined under applicable SEC rules.

Critical Accounting Policies and Significant Judgments and Estimates

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

While our significant accounting policies are described in more detail in the notes to our financial statements included elsewhere in this prospectus, 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

We recognize revenue for each unit of accounting when all of the following criteria are met: (i) persuasive evidence of an arrangement exists, (ii) delivery has occurred or services have been rendered, (iii) the seller's price to the buyer is fixed or determinable and (iv) collectability is reasonably assured.

The terms of our collaboration and license agreements contain multiple deliverables, which include licenses to CRISPR/Cas9-based therapeutic products directed to specific targets, referred to as exclusive licenses, as well as research and development activities to be performed by us on behalf of the collaboration partner related to the licensed targets. Payments that we may receive under these agreements include nonrefundable technology access fees, payments for research activities, payments based upon the achievement of specified milestones and royalties on any resulting net product sales.

Multiple Element Arrangements

We evaluate multiple-element arrangements to determine (i) the deliverables included in the arrangement and (ii) whether the individual deliverables represent separate units of accounting or whether they must be accounted for as a combined unit of accounting. When deliverables are separable, consideration received is allocated to the separate units of accounting based on the relative selling price method and the appropriate revenue recognition principles are applied to each unit. When we determine that an arrangement should be accounted for as a single unit of accounting, we must determine the period over which the performance obligations will be performed and revenue will be recognized. This evaluation requires us to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. Deliverables are considered separate units of accounting provided that (i) the delivered item has value to the customer on a standalone basis and (ii) the arrangement includes a general right of return with respect to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in our control. In assessing whether an item has standalone value, we consider factors such as the research, development, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, we consider whether the collaboration partner can use any other deliverable for its intended purpose without the receipt of the remaining deliverable, whether the value of the deliverable is dependent on the undelivered item, and whether there are other vendors that can provide the undelivered items.

The consideration received under an arrangement that is fixed or determinable is then allocated among the separate units of accounting based on the relative selling prices of the separate units of accounting. We determine the selling price of a unit of accounting within each arrangement using (i) vendor-specific objective evidence of selling price, if available; (ii) third-party evidence of selling price if vendor-specific objective evidence is not available; or (iii) best estimate of selling price, if neither vendor-specific objective evidence nor third-party evidence is available. Determining the best estimate of selling price for a unit of accounting requires significant judgment. In developing the best estimate of selling price for a unit of accounting, we consider applicable market

conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. We validate the best estimate of selling price for units of accounting by evaluating whether changes in the key assumptions used to determine the best estimate of selling price will have a significant effect on the allocation of arrangement consideration between multiple units of accounting.

We recognize arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria are satisfied for that particular unit of accounting. In the event that a deliverable does not represent a separate unit of accounting, we recognize revenue from the combined unit of accounting over the contractual or estimated performance period for the undelivered items, which is typically the term of our research and development obligations. If there is no discernible pattern of performance or objectively measurable performance measures do not exist, then we recognize revenue under the arrangement on a straight-line basis over the period we are expected to complete our performance obligations. Conversely, if the pattern of performance over which the service is provided to the customer can be determined and objectively measurable performance measures exist, then we recognize revenue under the arrangement using the proportional performance method. Revenue recognized is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method or proportional performance method, as applicable, as of the period ending date.

Significant management judgment is required in determining the level of effort required under an arrangement and the period over which we are expected to complete our performance obligations under an arrangement. Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if any, in determining the level of effort required in an arrangement and the period over which we expect to complete our aggregate performance obligations.

Recognition of Milestones and Royalties

Our collaboration and license agreements include contingent milestone payments related to specific development, regulatory and sales-based milestones. Development and regulatory milestones are typically payable when a product candidate initiates or advances in clinical trial phases, upon submission for marketing approval with regulatory authorities, and upon receipt of actual marketing approvals for a therapeutic or for additional indications. Sales-based milestones are typically payable when annual sales reach specified levels.

We evaluate whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether: (i) the consideration is commensurate with either our performance to achieve the milestone or the enhancement of the value of the delivered item as a result of a specific outcome resulting from our performance to achieve the milestone, (ii) the consideration relates solely to past performance and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. We evaluate factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the particular milestone and the level of effort and investment required to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether a milestone satisfies all of the criteria required to conclude that a milestone is substantive. We will recognize revenue in its entirety upon successful accomplishment of any substantive milestones, assuming all other revenue recognition criteria are met. Milestones that are not considered substantive are recognized as earned if there are no remaining performance obligations or over the remaining period of performance, with a cumulative catch-up being recognized for the elapsed portion of the period of performance, assuming all other revenue recognition criteria are met.

Nonrefundable research, development and regulatory milestones that are expected to be achieved as a result of our efforts during the period of our performance obligations under the collaboration and license agreements are generally considered to be substantive and are recognized as revenue upon the achievement of the milestone, assuming all other revenue recognition criteria are met. If not considered to be substantive, revenue from achievement of milestones is initially deferred and recognized over the remaining term of our performance obligations. Milestones that are not considered substantive because we do not contribute effort to their achievement are recognized as revenue upon achievement, assuming all other revenue recognition criteria are met, as there are no undelivered elements remaining and no continuing performance obligations on our part.

Amounts received prior to satisfying the revenue recognition criteria listed above are recorded as deferred revenue in the accompanying balance sheets. Although we follow detailed guidelines in measuring revenue, certain judgments affect the application of our revenue policy. For example, in connection with our existing collaboration agreement, we have recorded on the balance sheet short-term and long-term deferred revenue based on our best estimate of when such revenue will be recognized. However, this estimate is based on our current research plan and, if our research plan should change in the future, we may recognize a different amount of deferred revenue over the following 12-month period.

The estimate of deferred revenue also reflects management's estimate of the periods of our involvement in the collaboration. Our primary performance obligations under this collaboration consist of research and development services. In certain instances, the timing of satisfying these obligations can be difficult to estimate. Accordingly, our estimates may change in the future. Such changes to estimates would result in a change in prospective revenue recognition amounts. If these estimates and judgments change over the course of our collaborative agreement, it may affect the timing and amount of revenue that we will recognize and record in future periods.

Variable Interest Entities

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

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

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

As of December 31, 2016, TRACR is our wholly-owned subsidiary. See Note 4 to the consolidated financial statements for further details relating to the consolidation of TRACR as a VIE. For the year ended December 31, 2015, we consolidated the financial statements of TRACR into our consolidated financial statements as it was both a VIE and a majority owned subsidiary. For the year ended December 31, 2014, we consolidated TRACR as a VIE.

Equity-Based Compensation

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

We account for stock options issued to non-employees under FASB ASC Topic 505-50, Equity Based Payments to Non-Employees ("ASC 505-50"). As such, the value of such options is periodically remeasured and income or expense is recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected share price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of a public market for the trading of our Common Shares prior to its IPO and a lack of company-specific historical and implied volatility data, we based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies have characteristics similar to us, including stage of product development and focus on the life science industry. We use the simplified method, which is the average of the final vesting tranche date and the contractual term, to calculate the expected term for options granted to employees as it does not have sufficient historical exercise data to provide a

reasonable basis upon which to estimate the expected term. For options granted to non-employees, we utilize the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. We use an assumed dividend yield of zero as we have never paid dividends and has no current plans to pay any dividends on its Common Shares.

We expense the fair value of its equity-based compensation awards granted to employees on a straight-line basis over the associated service period, which is generally the period in which the related services are received. We measures equity-based compensation awards granted to non-employees at fair value as the awards vest and recognizes the resulting value as compensation expense at each financial reporting period.

We record the expense for equity-based compensation awards subject to performance-based milestone vesting over the remaining service period when management determines that achievement of the milestone is probable. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. There have only been eight such awards to date.

Recent Accounting Pronouncements

Refer to Note 2, “Summary of Significant Accounting Policies,” in the accompanying notes to the consolidated financial statements for a discussion of recent accounting pronouncements. There were no new accounting pronouncements adopted during 2016 that had a material effect on our financial statements.

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

Foreign Exchange Market Risk

As a result of our foreign operations, we face exposure to movements in foreign currency exchange rates, primarily the Swiss Franc and British Pound, against the U.S. dollar. The current exposures arise primarily from cash, accounts payable, and intercompany receivables and payables. Changes in foreign exchange rates affect our consolidated statement of operations and distort comparisons between periods. We do not engage in any foreign exchange rate hedging activities and therefore we are subject to foreign currency impacts.

Taxation

We are subject to corporate taxation in Switzerland.

Under Swiss law, we are entitled to carry forward losses we incur for a period of seven years and we can offset future profits, if any, against such losses. As of December 31, 2016, we reported tax loss carry forwards from inception through 2015 for purposes of Swiss federal direct taxes in the aggregate amount of CHF 22.0 million. Due to the accepted mixed company status (the tax ruling with respect to the mixed company status was accepted in February 2017 with retroactive effect as from 2013/2014) the tax losses available to offset future income at cantonal level amount to CHF 4.1 million. If not used, these tax losses will expire seven years after the year in which they occurred. Due to our limited income, there is a high risk that the tax loss carry forwards will expire partly or entirely. For 2016, the tax return has – in accordance with Swiss tax law – not yet been filed. Therefore, for 2016 the loss carried forward will only be claimed with filing of the tax return for the tax year 2016.

The statutory corporate profit tax rate in the Canton of Basel-Stadt where we are domiciled amounts (federal and cantonal) currently to a maximum of 28.5% on the profit after tax (taxes are deductible). We applied for a tax privilege as a mixed company for the years 2013/2014, 2015 and ongoing years. This application was confirmed in February 2017. According to the ruling confirmation, the corporate profit tax rate as mixed company amounts to 11.5% (federal and cantonal) on the profit after tax. The Canton does from time to time amend the level of taxation levied on corporations and there is no certainty that the tax rate currently in effect will not change in the future.

The privileges for mixed companies are under pressure and new tax legislations abolish mixed companies but at the same time lowering the ordinary tax rate is in preparation. Following the negative outcome of a revised tax legislation by a public vote on February 12, 2017, the scope and timing of such new tax legislation is uncertain.

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

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported, within the time periods specified in the Securities and Exchange Commission's rules and forms and (2) accumulated and communicated to our management, including our principal executive and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our disclosure controls and procedures are designed to provide reasonable assurance of achieving their control objectives.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2016. Based upon such evaluation, our Chief Executive Officer and Vice President of Finance have concluded that, as of December 31, 2016, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Controls Over Financial Reporting

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the Securities and Exchange Commission for newly public companies.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15(d)-15(f) under the Exchange Act) that occurred during the period covered by this Quarterly Report on Form 10-Q that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

On March 8, 2017, the Board of Directors of the Company approved the payout of annual incentive compensation to our executive officers, based upon the achievement of 95% of the corporate objectives set forth for 2016, as follows: Rodger Novak - $235,940; Marc Becker - $114,700; Samarth Kulkarni - $135,360; and Sven Ante (Bill) Lundberg - $131,600.

In addition, the Board of Directors also approved the metrics of the 2017 performance bonus program (the "2017 Program"). The 2017 Program is designed to motivate, retain and reward the Company's executive officers based on the achievement of both individual objectives and corporate objectives in 2017, including the achievement of certain intellectual property and budgetary goals, as well as clinical, research and development milestones. Each executive officer will be eligible to earn up to 135% of his or her target incentive annual compensation, which target is a percentage of his or her base salary.

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 2017 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2016.

Item 11. Executive Compensation.

The information required by this item is incorporated by reference to our Proxy Statement for our 2017 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2016.

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 2017 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2016.

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 2017 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2016.

Item 14. Principal Accounting Fees and Services.

The information required by this item is incorporated by reference to our Proxy Statement for our 2017 Annual General Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2016.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a)(1) Financial Statements.

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

(a)(2) Financial Statement Schedules.

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

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

(a)(3) Exhibits.

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

Item 16. Form 10-K Summary

None.

SIGNATURES

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

CRISPR Therapeutics AG

Date: March 10, 2017

By: /s/ Rodger Novak

Rodger Novak
Chief Executive Officer

SIGNATURES AND POWER OF ATTORNEY

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

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

Name	Title	Date
/s/ Rodger Novak Rodger Novak	Chief Executive Officer (Principal Executive Officer)	March 10, 2017
/s/ Marc A. Becker Marc A Becker	Chief Financial Officer (Principal Financial and Accounting Officer)	March 10, 2017
/s/ Anthony N. Coles Anthony N Coles	Director	March 10, 2017
/s/ Kurt Von Emster Kurt Von Emster	Director	March 10, 2017
/s/ Ali Behbahani Ali Behbahani	Director	March 10, 2017
/s/ Bradley Bolzon Bradley Bolzon	Director	March 10, 2017
/s/ Pablo Cagnoni Pablo Cagnoni	Director	March 10, 2017
/s/ Simeon J. George Simeon J. George	Director	March 10, 2017
/s/ Thomas Woiwode Thomas Woiwode	Director	March 10, 2017
/s/ Marc A. Becker Marc A. Becker	Authorized Representative in the United States	March 10, 2017

CRISPR Therapeutics AG

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Shareholders
CRISPR Therapeutics AG

We have audited the accompanying consolidated balance sheets of CRISPR Therapeutics AG (the "Company") as of December 31, 2016 and 2015, and the related consolidated statements of operations and comprehensive loss, redeemable convertible preferred shares and shareholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of CRISPR Therapeutics AG at December 31, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 10, 2017

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

	December 31,	
	2016	**2015**
Assets		
Current assets:		
Cash	$ 315,520	$ 155,961
Accounts receivable, including related party amounts of $752 and $0 as of December 31, 2016 and 2015, respectively	3,157	339
Prepaid expenses and other current assets	1,511	540
Total current assets	320,188	156,840
Property and equipment, net	21,027	1,328
Intangible assets, net	399	454
Restricted cash	3,150	700
Other non-current assets	198	101
Total assets	$ 344,962	$ 159,423
Liabilities, redeemable convertible preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 4,569	$ 1,584
Accrued expenses, including related party amounts of $537 and $1,055 as of December 31, 2016 and 2015, respectively	16,320	8,430
Accrued tax liabilities	23	81
Deferred rent	1,027	—
Other current liabilities	59	60
Total current liabilities	21,998	10,155
Convertible loan, including accrued interest of $0 and $97 as of December 31, 2016 and 2015, respectively	—	38,336
Deferred revenue, including related party amounts of $527 and $0 as of December 31, 2016 and 2015, respectively	77,646	75,090
Deferred rent non-current	12,283	164
Other non-current liabilities	189	281
Total liabilities	112,116	124,026
Commitments and contingencies (Note 8)		
Redeemable convertible preferred shares:		
Series A-1 redeemable convertible preferred shares, CHF 0.03 par value, 0 and 440,001 shares authorized, issued, and outstanding in share capital at December 31, 2016 and 2015, respectively, aggregate liquidation preference of CHF 0 and CHF 502 at December 31, 2016 and 2015, respectively	—	1,169
Series A-2 redeemable convertible preferred shares, CHF 0.03 par value, 0 and 3,120,001 shares authorized, issued, and outstanding in share capital at December 31, 2016 and 2015, respectively, aggregate liquidation preference of CHF 0 and CHF 9,512 at December 31, 2016 and 2015, respectively	—	10,394
Series A-3 redeemable convertible preferred shares, CHF 0.03 par value, 0 and 10,758,006 shares authorized, issued, and outstanding in share capital at December 31, 2016 and 2015, respectively, aggregate liquidation preference of $0 and $22,850 at December 31, 2016 and 2015, respectively	—	22,518
Series B redeemable convertible preferred shares, CHF 0.03 par value, 0 and 4,519,016 shares authorized, issued, and outstanding in share capital at December 31, 2016 and 2015, aggregate liquidation preference of CHF 0 and CHF 28,000 at December 31, 2016 and 2015, respectively	—	30,440
Shareholders' equity (deficit):		
Common shares, CHF 0.03 par value, 40,253,674, and 5,528,079 shares authorized at December 31, 2016 and 2015, respectively, 40,164,307 and 5,528,079 shares issued at December 31, 2016 and 2015, respectively, 39,719,434, and 5,528,079 shares outstanding at December 31, 2016 and 2015, respectively, 15,325,607 and 2,444,364 shares in conditional capital at December 31, 2016 and 2015, respectively	1,216	181
Treasury shares, at cost, 444,873 shares and no shares at December 31, 2016 and 2015, respectively	—	—
Additional paid-in capital	288,739	4,636
Accumulated deficit	(57,083)	(33,906)
Accumulated other comprehensive loss	(26)	(8)
Total CRISPR Therapeutics AG shareholders' equity (deficit)	232,846	(29,097)
Noncontrolling interest	—	(27)
Total shareholders' equity (deficit)	232,846	(29,124)
Total liabilities, redeemable convertible preferred shares and shareholders' equity (deficit)	$ 344,962	$ 159,423

See accompanying notes to these consolidated financial statements.

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

	Year Ended December 31,		
	2016	2015	2014
Collaboration revenue (1)	$ 5,164	$ 247	$ —
Operating expenses:			
Research and development (2)	42,238	12,573	1,513
General and administrative	31,056	13,403	5,114
Total operating expenses	73,294	25,976	6,627
Loss from operations	(68,130)	(25,729)	(6,627)
Other income (expense):			
Interest expense	(8,050)	(108)	—
Loss from equity method investment	(36,532)	—	—
Gain on extinguishment of convertible loan	11,482	—	—
Other income (expense), net	78,512	16	(236)
Total other income (expense), net	45,412	(92)	(236)
Net loss before (provision for) benefit from income taxes	(22,718)	(25,821)	(6,863)
(Provision for) benefit from income taxes	(484)	(7)	63
Net loss	(23,202)	(25,828)	(6,800)
Foreign currency translation adjustment	(18)	(6)	(2)
Comprehensive loss	$ (23,220)	$ (25,834)	$ (6,802)
Reconciliation of net loss to net loss attributable to common shareholders:			
Net loss	$ (23,202)	$ (25,828)	$ (6,800)
Loss attributable to noncontrolling interest	25	325	536
Loss on extinguishment of redeemable convertible preferred shares	—	—	(745)
Net loss attributable to common shareholders	$ (23,177)	$ (25,503)	$ (7,009)
Net loss per share attributable to common shareholders—basic and diluted	$ (1.89)	$ (5.06)	$ 1.97
Weighted-average common shares outstanding used in net loss per share attributable to common shareholders—basic and diluted	12,257,483	5,037,404	3,559,985
(1) Including the following amounts of revenue from a related party, see Note 16:	$ 1,190	$ —	$ —
(2) Including the following amounts of research and development from a related party, see Note 16:	$ 1,755	$ 1,055	$ —

See accompanying notes to these consolidated financial statements.

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

	Series A-1 Redeemable Convertible Preferred Shares		Series A-2 Redeemable Convertible Preferred Shares		Series A-3 Redeemable Convertible Preferred Shares		Series B Redeemable Convertible Preferred Shares		Common Shares		Treasury Shares						Total CRISPR Therapeutics AG Shareholders' (Deficit) Equity		Total Shareholders' (Deficit) Equity
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Shares	CHF 0.03 Par Value	Shares	Amount, at cost	Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)			Noncontrolling Interest	
Balance at December 31, 2013	440,001	$ 424	—	$ —	—	$ —	—	$ —	3,559,985	$ 98	—	—	$ 1,460	$ (2,139)	$ —		$ (581)	$ —	$ (581)
Receipt of common shares subscription receivable	—	—	—	—	—	—	—	—	—	22	—	—	—	—	—		22	—	22
Issuance of Series A-2 preferred shares, net of issuance costs of $36 and subscription receivable of $5,293	—	—	3,120,001	5,101	—	—	—	—	—	—	—	—	—	—	—		—	—	—
Loss on extinguishment of Series A-1 preferred shares	—	745	—		—	—	—	—	—	—	—	—	(745)	—	—		(745)	—	(745)
Other comprehensive income (loss)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(2)		(2)	—	(2)
Equity-based compensation expense	—	—	—	—	—	—	—	—	—	—	—	—	453	—	—		453	242	695
Noncontrolling interest upon consolidation of TRACR Hematology Limited	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		—	437	437
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	(6,264)	—		(6,264)	(536)	(6,800)
Balance at December 31, 2014	440,001	$ 1,169	3,120,001	$ 5,101	—	$ —	—	$ —	3,559,985	$ 120	—	—	$ 1,168	$ (8,403)	$ (2)		$ (7,117)	$ 143	$ (6,974)
Receipt of Series A-2 preferred shares subscription receivable	—	—	—	5,293	—	—	—	—	—	—	—	—	—	—	—		—	—	—
Issuance of Series A-3 preferred shares, net of issuance costs of $332 and subscription receivable of $22,850	—	—	—	—	10,758,006	22,518	—	—	—	—	—	—	—	—	—		—	—	—
Adjustment to noncontrolling interest upon share exchange transaction for TRACR Hematology Limited	—	—	—	—	—	—	—	—	1,968,094	61	—	—	1	—	—		62	(62)	—
Issuance of Series B preferred shares, net of issuance costs of $38	—	—	—	—	—	—	4,519,016	30,440	—	—	—	—	—	—	—		—	—	—
Equity-based compensation expense	—	—	—	—	—	—	—	—	—	—	—	—	3,467	—	—		3,467	217	3,684
Other comprehensive income (loss)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(6)		(6)	—	(6)
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	(25,503)	—		(25,503)	(325)	(25,828)
Balance at December 31, 2015	440,001	$ 1,169	3,120,001	$ 10,394	10,758,006	$ 22,518	4,519,016	$ 30,440	5,528,079	$ 181	—	—	$ 4,636	$ (33,906)	$ (8)		$ (29,097)	$ (27)	$ (29,124)
Conversion of Convertible Loans	—	—	—	—	—	—	5,464,608	61,929	—	—	—	—	—	—	—		—	—	—
Receipt of Series A-3 Subscription Receivable	—	—	—	—	—	22,850	—	—	—	—	—	—	—	—	—		—	—	—
Issuance of Series B Preferred Shares, net of issuance costs of $1.8 million	—	—	—	—	—	—	2,834,252	36,265	—	—	—	—	—	—	—		—	—	—
Conversion of redeemable convertible preferred shares into common share	(440,001)	(1,169)	(3,120,001)	(10,394)	(10,758,006)	(45,368)	(12,817,876)	(128,634)	27,135,884	823			184,742				185,565		185,565
Adjustment to Noncontrolling interest upon share exchange for TRACR	—	—	—	—	—	—	—	—	328,017	10			(62)				(52)	52	—
Issuance of common stock, net of issuance costs of $8.3 million	—	—	—	—	—	—	—	—	7,100,000	213			88,451				88,664		88,664
Repurchase of treasury shares	—	—	—	—	—	—	—	—	(444,873)	(13)	444,873	—	13	—	—		—	—	—
Vesting of restricted shares									53,427	1			81				82		82
Exercise of vested options	—	—	—	—	—	—	—	—	18,900	1	—	—	34	—	—		35	—	35
Stock- based compensation expense	—	—	—	—	—	—	—	—	—	—	—	—	10,844	—	—		10,844	—	10,844

Other comprehensive income (loss)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(18)	(18)	—	(18)
Net loss	—	—	—	—	—	—	—	—	—	—	—	—	—	—	(23,177)	—	(23,177)	(25)	(23,202)
Balance at December 31, 2016	—	$ —	—	$ —	—	$ —	—	$ —	39,719,434	$ 1,216	444,873	$ —	$ 288,739	$ (57,083)	$ (26)	$ 232,846	$ —	$ 232,846

See accompanying notes to these consolidated financial statements.

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

	Years Ended December 31,		
	2016	2015	2014
Operating activities			
Net loss	$ (23,202)	$ (25,828)	$ (6,800)
Reconciliation of net loss to net cash used in operating activities:			
Depreciation and amortization expense	925	127	38
Equity-based compensation expense	10,844	3,684	695
Non-cash interest expense	8,050	97	—
Unrealized foreign currency remeasurement loss	2	(20)	(260)
Gain on extinguishment of convertible loan	(11,482)	—	—
Other income - formation of joint venture	(78,608)	—	—
Loss from equity method investment	36,380	—	—
Changes in:			
Restricted cash	(2,450)	(650)	(16)
Accounts receivable	(2,818)	(339)	—
Prepaid expenses and other assets	(1,071)	(620)	(12)
Accounts payable and accrued expenses	3,860	7,708	1,583
Deferred revenue	1,917	75,090	—
Deferred rent	2,360	165	—
Other liabilities, net	(17)	14	(21)
Net cash (used in) provided by operating activities	(55,310)	59,428	(4,793)
Investing activities			
Purchase of property and equipment	(3,016)	(1,154)	—
Proceeds from contribution of intellectual property to equity method investee	35,000	—	—
Cash investment in equity method investee	(100)	—	—
Net cash provided by (used in) investing activities	31,884	(1,154)	—
Financing activities			
Proceeds from issuance of common shares in IPO, net of issuance costs	54,061	—	—
Proceeds from issuance of common shares in private placement	35,000	—	—
Proceeds from issuance of common shares	—	—	22
Proceeds from exercise of options	34	—	—
Proceeds from issuance of restricted shares	—	243	—
Proceeds from issuance of Series A-2 preferred shares	—	5,293	5,137
Proceeds from issuance of Series A-3 preferred shares	22,850	22,850	—
Proceeds from issuance of Series B preferred shares	38,075	30,478	—
Issuance costs for preferred share financings	(1,810)	(370)	(36)
Proceeds from issuance of convertible loans	35,010	38,239	—
Net cash provided by financing activities	183,220	96,733	5,123
Effect of exchange rate changes on cash	(235)	9	254
Increase in cash	159,559	155,016	584
Cash, beginning of period	155,961	945	361
Cash, end of period	$ 315,520	$ 155,961	$ 945
Supplemental disclosure of non-cash investing and financing activities			
Property and equipment purchases in accounts payable and accrued expenses	$ 7,014	$ 246	$ —
Property and equipment related to lease incentives	$ 10,785	$ —	$ —
Loss on extinguishment of Series A-1 preferred shares	$ —	$ —	$ 745
Noncontrolling interest upon consolidation of TRACR	$ —	$ —	$ 547
Conversion of preferred shares to common shares upon IPO	$ 185,565	$ —	$ —
Conversion of Vertex and Bayer convertible loans and accrued interest	$ 61,929	$ —	$ —
Issuance costs for public offering in accounts payable and accrued expenses	$ 397	$ —	$ —
Contribution of intellectual property to Casebia	$ 36,380	$ —	$ —

See accompanying notes to these consolidated financial statements.

1. Organization and Operations

Nature of business

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

On January 23, 2014, the founders of the Company formed TRACR Hematology Limited ("TRACR") in the United Kingdom, to further the development of the CRISPR/Cas9 technology into medicines for the treatment of blood-borne illnesses. As the Company was funding and managing TRACR's operations in 2014, it has been consolidated by the Company from the date that the Company established a variable interest in TRACR in April 2014. In March 2015, the Company acquired 82.1% of the outstanding equity of TRACR in a share exchange transaction. Concurrent with its initial public offering ("IPO") in October 2016, the Company acquired the outstanding non-controlling interest in TRACR as such, as of December 31, 2016 TRACR is a wholly-owned subsidiary of the Company.

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 $57.1 million as of December 31, 2016 and has financed its operations to date from proceeds obtained from its initial public offering a series of preferred shares and convertible loan issuances and upfront fees received under its collaboration and joint venture arrangements. The Company will require substantial additional capital to fund its research and development and ongoing operating expenses.

Liquidity

In October 2016, the Company completed the IPO of its common shares ("Common Shares"), in which the Company sold 4,429,311 Common Shares, inclusive of 429,311 Common Shares sold by the Company pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the offering, at a price of $14.00 per share. The shares began trading on the NASDAQ Global Market on October 19, 2016. The aggregate net proceeds received by the Company from the offering were $53.7 million (see Note 2) after deducting underwriting discounts and commissions and other offering expenses payable by the Company. Concurrent with the IPO, the Company issued and sold 2,500,000 Common Shares to Bayer Global Investments B.V. ("Bayer BV"), in a private placement, at the IPO price of $14.00 per share, for aggregate net proceeds of $35.0 million. Common Shares totaling 170,689 of the overallotment option granted by the underwriters in connection with the initial public offering were reacquired by the Company and are reflected as treasury shares on the consolidated balance sheet as of December 31, 2016. The Company believes its cash of $315.5 million at December 31, 2016 will be sufficient to fund the Company's current operating plan for at least the next 24 months. Thereafter, the Company will be required to obtain additional funding. There can be no assurances, however, that the current operating plan will be achieved or that additional funding will be available on terms acceptable to the Company, or at all.

2. Summary of Significant Accounting Policies and basis of presentation

Basis of Presentation and Use of Estimates

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"), and include the accounts of (i) the Company, (ii) its wholly-owned subsidiaries, CRISPR Ltd., CRISPR Inc., and TRACR, as of December 31, 2016. All intercompany accounts and transactions have been eliminated. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

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

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, equity-based compensation expense, revenue recognition, equity method investments, and reported amounts of expenses during the reported period. Significant estimates in these consolidated financial statements have been made in connection with the calculation of revenues, research and development expenses, valuation of equity method of investment, equity-based compensation expense, fair value of Common Shares, fair value of intangible assets, and the provision for or benefit from income taxes. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Actual results may differ from those estimates or assumptions.

The Company utilizes significant estimates and assumptions in determining the fair value of its Common Shares. The Company utilized various valuation methodologies in accordance with the framework of the 2004 and 2013 American Institute of Certified Public Accountants Technical Practice Aids, *Valuation of Privately- Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its Common Shares. Each valuation methodology includes estimates and assumptions that require the Company's judgment. These estimates and assumptions include a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector, the prices at which the Company sold shares of preferred stock, the superior rights and preferences of securities senior to the common stock at the time and the likelihood of achieving a liquidity event, such as an initial public offering or sale. Significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date. Subsequent to becoming a public company, the Company uses the closing price of its stock on the Nasdaq Global Market as the fair value of its common stock.

Reclassifications

A change has been made to the presentation of deferred rent non-current as of December 31, 2015 to conform to the current year presentation.

Stock Split

In connection with preparing for its IPO, the Company's board of directors and shareholders approved an amendment to the Company's articles of association in July 2016. This amendment became effective upon registration in the Switzerland commercial register on July 27, 2016 and publication in the Swiss Official Gazette of Commerce on August 2, 2016. Pursuant to this amendment a $3\ ^1/_3$-for-one share split was effected. All share and per share amounts in the consolidated financial statements and notes thereto have been retrospectively adjusted for all periods presented to give effect to the share split.

Segment Information

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

Foreign Currency Translation and Transactions

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

Cash and Cash Equivalents

The Company considers all highly liquid investments with maturities of 90 days or less from the purchase date to be cash equivalents. As of December 31, 2016, and 2015, the Company had $315.5 million and $156.0 million in cash equivalents, respectively. All cash was held in depository accounts and is reported at fair value.

Accounts Receivable

Accounts receivable of $3.2 million at December 31, 2016 consist of receivables from Vertex Pharmaceuticals, Incorporated ("Vertex") and Casebia. As of December 31, 2015, the Company had accounts receivable of $0.3 million consisting of receivables from Vertex. Accounts receivables are recorded at invoiced amounts due under both the Vertex and Casebia collaboration agreements (see Note 9). Vertex and Casebia are creditworthy entities that maintain an ongoing relationship with the Company, as such the Company did not have an allowance for estimated losses recorded related to these receivables.

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.

Deferred Public Offering Costs

Deferred public offering costs, which primarily consist of direct, incremental legal and accounting fees relating to the IPO, were capitalized within other non-current assets prior to our IPO. The issuance costs of $8.3 million, including underwriter's commissions, were offset against the IPO proceeds upon the consummation of the offering in October 2016.

Fair Value of Financial Instruments

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

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

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

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

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

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

The carrying amount of accounts receivable, accounts payable, and accrued expenses as reported on the consolidated balance sheets as of December 31, 2016 and 2015, approximate fair value, due to the short-term duration of these instruments.

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

Property and Equipment

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

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

Impairment of Long-lived Assets

The Company evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparing the book value of the assets to the expected future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book value of the assets exceed their fair value. The Company has not recognized any impairment losses in the years ended December 31, 2016, 2015, and 2014.

Revenue Recognition

To date, the Company's only source of revenue has been the collaboration and license agreement with Vertex as well as research and development services provided to Casebia under the joint venture with Bayer HealthCare LLC ("Bayer") (see Note 9).

The Company recognizes revenue in accordance with ASC Topic 605, *Revenue Recognition* ("ASC 605"). Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

- Persuasive evidence of an arrangement exists;
- Delivery has occurred or services have been rendered;
- The seller's price to the buyer is fixed or determinable; and
- Collectability is reasonably assured.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified in current liabilities. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue within non-current liabilities.

The Company evaluates multiple-element arrangements based on the guidance in FASB ASC Topic 605-25, *Revenue Recognition—Multiple-Element Arrangements* ("ASC 605-25"). Pursuant to the guidance in ASC 605-25, the Company evaluates multiple-element arrangements to determine (i) the deliverables included in the arrangement and (ii) whether the individual deliverables represent separate units of accounting or whether they must be accounted for as a combined unit of accounting. When deliverables are separable, consideration received is allocated to the separate units of accounting based on the relative selling price method and the appropriate revenue recognition principles are applied to each unit. When the Company determines that an arrangement should be accounted for as a single unit of accounting, the Company must determine the period over which the performance obligations will be performed and revenue will be recognized. This evaluation requires the Company to make judgments about the individual deliverables and whether such deliverables are separable from the other aspects of the contractual relationship. Deliverables are considered separate units of accounting provided that (i) the delivered item has value to the collaboration partner on a standalone basis and (ii) if the arrangement includes a general right of return with respect to the delivered item, delivery or performance of the undelivered item is considered probable and substantially in the Company's control. In assessing whether an item has standalone value, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the collaboration partner can use any other deliverable for its intended purpose without the receipt of the remaining deliverable, whether the value of the deliverable is dependent on the undelivered item, and whether there are other vendors that can provide the undelivered items.

The consideration received under the arrangement that is fixed or determinable is then allocated among the separate units of accounting based on the relative selling prices of the separate units of accounting. The Company determines the selling price of a unit of accounting within each arrangement following the hierarchy of evidence prescribed by ASC 605-25. Accordingly, the Company determines the estimated selling price for units of accounting within each arrangement using vendor-specific objective evidence ("VSOE") of selling price, if available; third-party evidence ("TPE") of selling price if VSOE is not available; or best estimate of selling price ("BESP") if neither VSOE nor TPE is available. The Company typically uses BESP to estimate the selling price as it generally does not have VSOE or TPE of selling price for its units of accounting. Determining the BESP for a unit of accounting requires significant judgment. In developing the BESP for a unit of accounting, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. The Company periodically validates the BESP used for units of accounting by evaluating whether changes in the key assumptions used to determine the BESP will have a significant effect on the allocation of arrangement consideration between multiple units of accounting.

The Company recognizes arrangement consideration allocated to each unit of accounting when all of the following criteria are met for that particular unit of accounting: persuasive evidence of an arrangement exists, delivery has occurred or services have been rendered, the seller's price to the buyer is fixed or determinable, and collectability is reasonably assured. In the event that a deliverable does not represent a separate unit of accounting, the Company recognizes revenue from the combined unit of accounting over the contractual or estimated performance period for the undelivered items, which is typically the term of the Company's research and development obligations. If there is no discernible pattern of performance or objectively measurable performance measures do not exist, then the Company recognizes revenue under the arrangement on a straight-line basis over the period the Company is expected to complete its performance obligations. Conversely, if the pattern of performance over which the service is provided to the customer can be determined and objectively measurable performance measures exist, then the Company recognizes revenue under the arrangement using the proportional performance method. Revenue recognized is limited to the lesser of the cumulative amount of payments received or the cumulative amount of revenue earned, as determined using the straight-line method or proportional performance method, as applicable, as of the period ending date.

Significant management judgment is required in determining the level of effort required under an arrangement and the period over which the Company expects to complete its performance obligations under an arrangement. Steering committee services that are not inconsequential or perfunctory and that are determined to be performance obligations are combined with other research services or performance obligations required under an arrangement, if any, in determining the level of effort required in an arrangement and the period over which the Company expects to complete its aggregate performance obligations.

At the inception of an arrangement that includes milestone payments, the Company evaluates whether each milestone is substantive and at risk to both parties on the basis of the contingent nature of the milestone. This evaluation includes an assessment of whether: (i) the consideration is commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (ii) the consideration relates solely to past performance, and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company evaluates factors such as the scientific, clinical, regulatory, commercial and other risks that must be overcome to achieve the particular milestone and the level of effort and investment required to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether a milestone satisfies all of the criteria required to conclude that a milestone is substantive. The Company will recognize revenue in its entirety upon successful accomplishment of any substantive milestones, assuming all other revenue recognition criteria are met. Milestones that are not considered substantive are recognized as earned if there are no remaining performance obligations or over the remaining period of performance, with a cumulative catch-up being recognized for the elapsed portion of the period of performance, assuming all other revenue recognition criteria are met.

The Company will recognize royalty revenue in the period of sale of the related product(s), based on the underlying contract terms, provided that the reported sales are reliably measurable and the Company has no remaining performance obligations, assuming all other revenue recognition criteria are met.

Research and Development Expenses

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

Operating Leases

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

Equity Based Compensation Expense

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

The Company accounts for stock options issued to non-employees under FASB ASC Topic 505-50, *Equity Based Payments to Non-Employees* ("ASC 505-50"). As such, the value of such options is periodically remeasured and income or expense is recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method.

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

The Company expenses the fair value of its equity-based compensation awards granted to employees on a straight-line basis over the associated service period, which is generally the period in which the related services are received. The Company measures equity-based compensation awards granted to non-employees at fair value as the awards vest and recognizes the resulting value as compensation expense at each financial reporting period.

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

Patent Costs

Costs to secure and prosecute patent application and other legal costs related to the protection of the Company's intellectual property are expensed as incurred, and are classified as general and administrative expenses in the Company's consolidated statements of operations.

Income Taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, *Income Taxes* ("ASC 740"), which provides for deferred taxes using an asset and liability approach. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and tax reporting basis of assets and liabilities and are measured using enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. The Company has evaluated available evidence and concluded that the Company may not realize all the benefit of its deferred tax assets; therefore a valuation allowance has been established for the amount of the deferred tax assets that the Company does not believe is more likely than not to be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2016 and 2015, the Company does not have any significant uncertain tax positions. The Company's practice is to recognize interest and/or penalties related to income tax matters in income tax expense. See Note 14 for further details.

Comprehensive Loss

Comprehensive loss consists of net income or loss and changes in equity during the period from transactions and other events and circumstances generated from non-owner sources. The Company's net loss equals comprehensive loss, net of any changes in the foreign currency translation adjustment, for all periods presented. In addition, comprehensive loss attributable to the noncontrolling interest equals net loss for all periods presented.

Variable Interest Entities

The Company reviews each legal entity formed by parties related to the Company to determine whether or not the Company has a variable interest in the entity and whether or not the entity would meet the definition of a VIE in accordance with FASB ASC Topic 810, *Consolidation* ("ASC 810"). If the entity is a VIE, the Company assesses whether or not the Company is the primary beneficiary of that VIE based on a number of factors, including (i) which party has the power to direct the activities that most significantly affect the VIE's economic performance, (ii) the parties' contractual rights and responsibilities pursuant to any contractual agreements and (iii) which party has the obligation to absorb losses or the right to receive benefits from the VIE. If the Company determines it is the primary beneficiary of a VIE, the Company consolidates the financial statements of the VIE into the Company's consolidated financial statements at the time that determination is made. The Company evaluates whether it continues to be the primary beneficiary of any consolidated VIEs on a quarterly basis. If the Company were to determine that it is no longer the primary beneficiary of a consolidated VIE, or no longer has a variable interest in the VIE, it would deconsolidate the VIE in the period that the determination is made.

If the Company determines it is the primary beneficiary of a VIE that meets the definition of a business, the Company measures the assets, liabilities and noncontrolling interests of the newly consolidated entity at fair value in accordance with FASB ASC Topic 805, *Business Combinations* ("ASC 805") at the date the reporting entity first becomes the primary beneficiary.

In February 2016, Casebia Therapeutics LLP, a limited liability partnership, was formed in the United Kingdom. In March 2016 upon consummation of the JV, Bayer and the Company each received a 50% equity interest in the entity in exchange for their contributions to the entity. The Company determined that Casebia was considered a VIE and concluded that it is not the primary beneficiary of the VIE. As such, the Company did not consolidate Casebia's results into the consolidated financial statements. See Note 4 for further details.

As of December 31, 2016, TRACR is a wholly-owned subsidiary of the Company. See Note 4 for further details. For the year ended December 31, 2015, the Company consolidated the financial statements of TRACR into the Company's consolidated financial statements as it was both a VIE and a majority owned subsidiary. For the year ended December 31, 2014, the Company consolidated TRACR as a VIE.

Noncontrolling Interest

Upon the IPO date of the Company, the non-controlling interest of TRACR was acquired, and as of the year ended December 31, 2016 TRACR is a wholly-owned subsidiary of the Company. See Note 4 for further details related to TRACR. The Company recorded non-controlling interest, which was related to TRACR during 2015 and 2016. The Company recorded net loss attributable to non-controlling interest on its consolidated statements of operations, reflecting the loss from non-controlling interest for the reporting period.

Intangible Assets

The Company's intangible assets consist of acquired intellectual property rights and relate to the Company's interest in TRACR. Intangible assets are recorded at fair value at the date of the business combination and are stated in the consolidated balance sheets net of accumulated amortization and impairments, if applicable. The Company evaluates the remaining useful life of intangible assets subject to amortization on a periodic basis to determine whether events and circumstances would indicate impairment or warrant a revision to the remaining useful life. If the estimate of an intangible asset's remaining useful life is changed, the Company amortizes the remaining carrying value of the intangible asset prospectively over the revised remaining useful life.

Intangible assets related to the acquired intellectual property rights are amortized over their estimated useful lives using the straight-line method as the pattern of revenues cannot be reasonably estimated. Amortization related to the acquired intellectual property rights is recorded in general and administrative expense in the consolidated statements of operations and comprehensive loss.

Net Loss Per Share Attributable to Common Shareholders

Basic net income (loss) per share is calculated by dividing net income (loss) attributable to common shareholders by the weighted-average number of common shares outstanding during the period. Diluted net income per share is calculated by dividing the net income attributable to common shareholders by the weighted-average number of common equivalent shares outstanding for the period, including any dilutive effect from outstanding stock options and warrants using the treasury stock method.

The Company follows the two-class method when computing net income per share in periods when participating securities are outstanding. The two-class method determines net income per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common shareholders for the period to be allocated between common and participating securities based on their respective rights to receive dividends as if all income for the period had been distributed. Accordingly, in periods in which the Company reports a net loss attributable to common shareholders when participating securities are outstanding, losses are not allocated to the participating securities because they have no contractual obligation to share in the losses of the Company. For purposes of calculating diluted net income per share attributable to redeemable preferred shares, convertible loans, stock options, and unvested restricted common shares are considered common share equivalents.

The following table sets forth the outstanding potentially dilutive securities that have been excluded in the calculation of diluted net loss per share because to do so would be anti-dilutive (in common stock equivalent shares):

	As of December 31,		
	2016	2015	2014
Convertible preferred shares	—	18,837,024	3,560,002
Conversion of convertible loans	—	4,110,987	—
Dr. Emmanuelle Charpentier call option	—	328,017	—
Outstanding options	4,535,371	1,939,986	—
Unvested unissued restricted shares	89,367	142,794	—
Total	4,624,738	25,358,808	3,560,002

Subsequent Events

The Company considered the events or transactions occurring after the balance sheet date, but prior to the issuance of the consolidated financial statements, for potential recognition or disclosure in its consolidated financial statements. All significant subsequent events have been properly disclosed in the consolidated financial statements.

Recent Accounting Pronouncements

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers* (Topic 606) ("ASU 2014-09"). Subsequently, the FASB also issued ASU 2015-14, *Revenue from Contracts with Customers* (Topic 606), which adjusted the effective date of ASU 2014-09; ASU No. 2016-08, *Revenue from Contracts with Customers* (Topic 606): Principal versus Agent Considerations (Reporting Revenue Gross versus Net), which amends the principal-versus-agent implementation guidance and illustrations in ASU 2014-09; ASU No. 2016-10, *Revenue from Contracts with Customers* (Topic 606): Identifying Performance Obligations and Licensing, which clarifies identifying performance obligation and licensing implementation guidance and illustrations in ASU 2014-09; and ASU No. 2016-12, *Revenue from Contracts with Customers* (Topic 606): Narrow-Scope Improvements and Practical Expedients, which addresses implementation issues and is intended to reduce the cost and complexity of applying the new revenue standard in ASU 2014-09 (collectively, the "Revenue ASUs").

The Revenue ASUs provide an accounting standard for a single comprehensive model for use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance. The accounting standard is effective for interim and annual periods beginning after December 15, 2017, with an option to early adopt for interim and annual periods beginning after December 15, 2016. The guidance permits two methods of adoption: retrospectively to each prior reporting period presented (the full retrospective method), or retrospectively with the cumulative effect of initially applying the guidance recognized at the date of initial application (the modified retrospective method). We currently anticipate adoption of the new standard effective January 1, 2018 under the full retrospective method. The Company is in the process of determining the impact of the Revenue ASUs on its financial statements.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements—Going Concern* (Subtopic 205-40): Disclosure of Uncertainties about an Entity's ability to Continue as a Going Concern ("ASU 2014-15"), which requires management to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. This guidance is effective for the annual reporting period ending after December 15, 2016 and for annual and interim periods thereafter. The Company adopted ASU 2014-15 on December 31, 2016 and the adoption of ASU 2014-15 did not have an effect on our consolidated financial statements or disclosures.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* ("ASU 2016-02"), which applies to all leases and will require lessees to record most leases on the balance sheet, but recognize expense in a manner similar to the current standard. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 and interim periods within those years, which is the year ended December 31, 2019 for the Company. Entities are required to use a modified retrospective approach of adoption for leases that exist or are entered into after the beginning of the earliest comparative period in the financial statements. Full retrospective application is prohibited. The Company is evaluating the new guidance and the expected effect on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, Compensation—*Stock Compensation (Topic 718)* ("ASU 2016-09"). The guidance changes how companies account for certain aspects of equity-based payments to employees. Entities will be required to recognize income tax effects of awards in the income statement when the awards vest or are settled. The guidance also allows an employer to repurchase more of an employee's shares than it can under current guidance for tax withholding purposes providing for withholding at the employee's maximum rate as opposed to the minimum rate without triggering liability accounting and to make a policy election to account for forfeitures as they occur. The updated guidance is effective for annual periods beginning after December 15, 2017. Early adoption is permitted. Under today's guidance, the Company does not recognize the income tax effects of awards that have vested or are settled until they actually reduce taxes payable. This standard will require the Company to recognize these effects when they are vested or are settled, subject to the assessment of the need for a valuation allowance. The adoption of this standard is not expected to have a material impact on the Company's financial position, results of operations or statements of cash flows upon adoption, primarily because any tax effects the Company may be required to realize are expected to be subject to a full valuation allowance.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* ("ASU 2016-08"). ASU 2016-18 requires that a statement of cash flows explain the change during the period in the total cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning and ending balances shown on the statement of cash flows. The guidance is effective in the first quarter of fiscal 2018 and early adoption is permitted. ASU 2016-18 must be applied retrospectively to all periods presented. Upon adoption, the Company's 2016 statement of cash flows will reflect an increase in operating cash flows resulting from the adoption of this new standard. The Company does not expect any additional impact on its financial statements.

3. Property and Equipment, net

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

	As of December 31,	
	2016	2015
Computer equipment and software	$ 110	$ 118
Furniture, fixtures, and other	2,044	238
Laboratory equipment	2,970	861
Leasehold improvements	15,780	88
Construction work in process	1,065	95
	21,969	1,400
Accumulated Depreciation	(942)	(72)
Property and equipment, net	$ 21,027	$ 1,328

Depreciation expense for the year ended December 31, 2016, 2015, and 2014 was $0.9 million, $0.1 million, and $0 million, respectively.

4. Variable Interest Entities

TRACR Hematology Limited

On January 23, 2014, the founders of the Company formed TRACR in the United Kingdom, to further the development of the CRISPR/Cas9 technology into medicines for the treatment of blood-borne illnesses. On April 14, 2014, TRACR licensed certain foundational intellectual property rights under joint ownership from Dr. Emmanuelle Charpentier to develop and commercialize products for the treatment or prevention of human diseases related to hemoglobinopathies. See Note 9 for further details of the technology license agreement with Dr. Charpentier.

On April 14, 2014 the Company determined that it became the primary beneficiary of TRACR based on, among other factors, the Company's power to direct the activities that significantly impacted the economic performance of TRACR and the Company's financing of contractual obligations on behalf of TRACR, and the period in which the Company began to benefit from research and development of TRACR technology. Accordingly, the Company consolidated TRACR's financial statements as a consolidated VIE beginning on April 14, 2014.

On March 24, 2015, the Company acquired 4,600 ordinary shares of TRACR, representing 82.1% of the ordinary share capital, pursuant to a share exchange transaction with the shareholders of TRACR. In exchange for 4,600 ordinary shares of TRACR and the assignment of certain rights to subscribe ordinary shares of TRACR, the Company issued 852,846 Common Shares to two founders of TRACR, 656,031 restricted Common Shares to certain employees and non-employees, and 459,217 Common Shares to Fay Participation Corporation ("Fay Corp."), an entity formed to hold Common Shares for future issuance to certain employees and non-employees. As of December 31, 2015, the Company held 4,600 ordinary shares of TRACR, representing 82.1% of the ordinary share capital of TRACR.

Upon the share exchange on March 24, 2015, the Company recorded an adjustment of $0.1 million to decrease the carrying amount of the noncontrolling interest in TRACR and reflect the Company's increased ownership interest in TRACR's net assets. This adjustment was recognized directly in equity through additional paid-in capital and is attributable to the controlling interest.

Pursuant to the share exchange transaction on March 24, 2015, the Company also entered into a freestanding call option agreement with Dr. Charpentier for 1,000 ordinary shares of TRACR, representing the remaining 17.9% of the ordinary share capital of TRACR. Under the terms of the call option agreement, the Company has the option to acquire the remaining 1,000 shares of TRACR held by Dr. Charpentier in exchange for 328,017 Common Shares of the Company. In the event the option is exercised by the Company prior to a liquidation event, the Company will indemnify Dr. Charpentier for all taxes owed as a result of the exchange. In addition, upon a bankruptcy, liquidation, closing of an IPO, winding up of the Company, a change in control or other deemed liquidation event, as defined in the call option agreement, the remaining 1,000 ordinary shares of TRACR held by Dr. Charpentier will automatically convert into 328,017 Common Shares of the Company. The call option was determined to have a fair value of $0.2 million at the time of the share exchange and was attributed to Dr. Charpentier's for past services rendered to CRISPR and TRACR. Upon IPO, the call option was exercised and the remaining non-controlling interest of TRACR was acquired, resulting in a reduction of Noncontrolling interest of $0.1 million, stock based compensation of $0.2 million for original value of the call option, and additional paid-in capital of $0.1 million.

Joint Venture with Bayer Healthcare LLC

In December 2015, the Company entered into an agreement with Bayer to create a joint venture to discover, develop and commercialize new therapeutics for genetically linked diseases, including blood disorders, blindness and heart disease. On February 12, 2016, Casebia, a limited liability partnership, was formed in the United Kingdom. In March 2016 upon consummation of the JV, Bayer and the Company each received a 50% equity interest in the entity in exchange for their contributions to the entity. The Company determined that Casebia was considered a VIE and concluded that it is not the primary beneficiary of the VIE. As such, the Company did not consolidate Casebia's results into the consolidated financial statements. See Note 9 for further details.

5. Intangible Assets

The Company's intangible assets consist of acquired intellectual property rights related to the Company's initial consolidation of TRACR in April 2014. Acquired intellectual property rights had an estimated life of 10 years. Intangible assets, net of accumulated amortization, are as follows (in thousands):

Acquired intangible asset	Cost	Accumulated Amortization	Net
As of December 31, 2016	$ 547	$ (148)	$ 399
As of December 31, 2015	$ 547	$ (93)	$ 454

The Company recorded amortization expense of $0.1 million, $0.1 million, and $40 thousand for each of the years ended December 31, 2016, 2015, and 2014, respectively. As of December 31, 2016 and 2015, the remaining amortization period was 7.3 years and 8.3 years, respectively. The Company has not recorded any impairment charges for the years ended December 31, 2016, 2015 and 2014. The estimated future amortization of acquired intangible assets as of December 31, 2016 is expected to be as follows (in thousands):

Year Ending December 31:	Amount
2017	$ 55
2018	55
2019	55
2020	55
Thereafter	179
Total amortization	$ 399

6. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31, 2016	2015
Payroll and employee-related costs	$ 2,585	$ 773
Research costs	996	910
Licensing fees	492	1,055
Professional fees	2,715	2,412
Intellectual property costs	3,372	2,592
Accrued property and equipment	5,081	—
Other	1,079	688
Total	$ 16,320	$ 8,430

7. Convertible Loans

2015 Convertible Loan Agreement with Vertex and certain existing shareholders

On October 26, 2015, the Company entered into a convertible loan agreement with Vertex and certain existing shareholders (the "Vertex Convertible Loan") under which the Company could borrow up to $40.0 million. The Vertex Convertible Loan accrues interest at 2.5% per annum and had an initial maturity date of April 26, 2016 subject to acceleration upon the occurrence of certain conditions stated in the loan agreement (the "Maturity Date"). On various dates between November 23 and December 7, 2015, the Company borrowed aggregate net proceeds of $38.2 million. The Vertex Convertible Loan included various embedded conversion, redemption and other features, as further described below, none of which required separate accounting from the host instrument under ASC 815. On January 29, 2016, all of the outstanding principal plus accrued interest of $0.2 million under the Vertex Convertible Loan was automatically converted into 2,859,278 Series B Preferred Shares in connection with a qualified financing described below.

An event of default ("Event of Default") is defined in the Vertex Convertible Loan Agreement and includes events of bankruptcy, insolvency or reorganization and, solely at the election of Vertex, a material breach that is not cured within the applicable notice and cure periods of the strategic collaboration, option and license agreement entered into by Vertex and the Company. See Note 9 for further details of the strategic, option and license agreement.

Conversion Terms

On the Maturity Date, the outstanding principal plus accrued interest automatically converts into Series B Preferred Shares at $9.33 per share.

In the event the Company issues equity securities prior to the Maturity Date with aggregate proceeds of not less than $50.0 million, of which $5.0 million is raised from investors other than Vertex or existing shareholders, the outstanding principal plus accrued interest under the Vertex Convertible Loan automatically converts into the newly issued equity securities at the price per share paid by the investors in the financing.

In the event of an underwritten public offering with shares of the Company listed on the New York Stock Exchange, the NASDAQ Global Market, or the NASDAQ Global Market, resulting in at least $50.0 million of proceeds to the Company closed prior to Maturity, the holders may elect, prior to the closing of the IPO, to convert the outstanding principal plus accrued interest into Series B Preferred Shares at $9.33 per share. Any Vertex Convertible Loan not converted prior to the closing of the IPO, shall automatically convert into Common Shares at a price paid by the investors for such shares in the IPO.

Upon a liquidation event prior to the Maturity Date, the holders may elect to convert the outstanding principal plus accrued interest into either Common Shares at a price of $9.33 per share or Series B Preferred Shares at a price of $9.33 per share.

Redemption Terms

Upon an Event of Default, all outstanding principal plus accrued interest becomes immediately due and payable.

Upon a liquidation event, if the holders do not exercise their conversion right, the outstanding principal plus accrued interest shall become due and payable in cash on the business day following the date on which the Company or its shareholders receive the proceeds from the liquidation event.

Contingent Interest

Upon an Event of Default, the outstanding amount of the Vertex Convertible Loan shall bear, in addition to the base interest of 2.5% per annum, default interest at a rate of 7.5% per annum.

Convertible Loan with Bayer HealthCare LLC

Concurrent with the execution of the Bayer Joint Venture agreement, the Company also entered into a Convertible Loan Agreement ("Bayer Convertible Loan") with Bayer for $35.0 million. The Bayer Convertible Loan accrued interest at 2.0% per annum and matured on January 29, 2016 (the "Maturity Date"). On January 29, 2016, the Company issued the Bayer Convertible Loan in exchange for aggregate net proceeds of $35.0 million. The Bayer Convertible Loan included various embedded conversion, redemption and other features, none of which required separate accounting from the host instrument under ASC 815.

Conversion of Convertible Loans to Series B Preferred Shares

On January 29, 2016, concurrent with the issuance of the Bayer Convertible Loan, all of the outstanding principal under the $35.0 million Bayer Convertible Loan automatically converted into 2,605,330 Series B Preferred Shares at $13.43 per share. The Company determined the fair value of the Bayer Convertible Loan to be $24.5 million based on the fair value of the underlying Series B Preferred Shares that were exchanged as part of the immediate conversion. As the Bayer Convertible Loan was executed in contemplation of the joint venture agreement with Bayer, the Company evaluated the Bayer Convertible Loan as part of one multiple-element arrangement and using a relative fair value allocation allocated $27.0 million of aggregate arrangement consideration to the Bayer Convertible Loan upon issuance (See Note 9). Upon conversion, the Company accreted the Bayer Convertible Loan to its face value of $35.0 million through a charge to interest expense of $8.0 million and converted the $35.0 million to Series B Preferred Shares under the conversion model.

The receipt of $35.0 million in proceeds under the Bayer Convertible Loan in exchange for equity securities, combined with the $38.2 million in proceeds from Vertex Convertible Loan, triggered an automatic conversion provision of the Vertex Convertible Loan Agreement. Accordingly, on January 29, 2016, the Vertex Convertible Loan, including loans from existing shareholders, plus accrued interest also converted into 2,859,278 of Series B Preferred Shares at $13.43 per share. The Company determined the fair value of the Vertex Convertible Loan to be $26.9 million based on the fair value of the underlying Series B Preferred Shares that were exchanged as part of the conversion. Upon extinguishment, the Company recorded a gain on extinguishment of $11.5 million for the difference between the carrying value of the debt and the fair value of the Series B Preferred Shares issued to settle the debt under the general extinguishment model.

8. Commitments and Contingencies

Operating Leases

As of December 31, 2016, the Company had five non-cancellable operating leases for office, laboratory, and corporate housing spaces during the year ended December 31, 2016. Three of the leases expire in 2017. The lease of the Company's research facility space expires in February 2022, with one optional five-year extension period. The sublease of the Company's primary office and research facility space expires in December 2026. Rental expense for the years ended December 31, 2016, 2015, and 2014 was $4.2 million, $1.3 million, and $17 thousand, respectively. The Company expenses rent, including tenant improvement allowances received by the Company, on a straight-line basis over the term of the lease, including any rent-free periods.

In April 2015, the Company entered into a lease for laboratory and office lease facilities in Cambridge, Massachusetts (the "200 Sidney Street Lease"). The 200 Sidney Street Lease lease expires in February 2022 with one additional five year extension period. The 200 Sidney Street Lease contains escalating rent clauses which require higher rent payments in future years.

In June 2015, the Company entered into an agreement pursuant to which it has the right to use certain office facilities in London England. The current term expires in July 2017. The Company's obligations under this right to use agreement are secured by a cash deposit in the approximate amount of GBP 9 thousand held by the office space provider.

In October 2015, the Company entered into a lease for corporate housing in Cambridge, Massachusetts. The term of the original lease was renewed in November 2016 and the current term expires in November 2017 subject to additional one year renewals. The Company's obligations under the terms of this lease are secured by a cash deposit in the approximate amount of $10 thousand held by the lessor.

In April 2016, the Company entered into a sublease for office facilities in Cambridge Massachusetts. The Company' obligations under the terms of this lease were secured by a cash deposit in the approximate amount of $26 thousand held by the lessor. This lease term expired in January 2017.

In May 2016, the Company entered into a sublease pursuant to which it subleases in Cambridge, Massachusetts (the "610 Main Street Sublease") the Company's primary research and US office facility. The initial term of the 610 Main Street will expire on December 22, 2026. The Company has an option to extend the term of the 610 Main Street 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 610 Main Street Sublease contains escalating rent clauses which require higher rent payments in future years.

The 610 Main Street Sublease included a $10.8 million tenant improvements allowance for normal tenant improvements, for which construction began in June 2016. The date of the construction coincided with the lease commencement date for accounting purposes under ASC 840, *Leases*. The Company recorded straight-line rent expense of $2.3 million during the year ended December 31, 2016 and a deferred rent liability of $12.9 million, inclusive of a tenant improvement allowance of $10.2 million which the Company is amortizing as a reduction of rent expense over the sublease term. As of December 31, 2016, $1.0 million of the tenant improvement allowance was recorded within current deferred rent, and the remaining $11.9 million as non-current deferred rent on the consolidated balance sheet.

In May 2016, the Company entered a $2.5 million letter of credit to secure the Company's obligations under the 610 Main Street Sublease. The letter of credit is secured by cash held in a restricted depository account. The deposit is recorded in restricted cash in the accompanying consolidated balance sheet as of December 31, 2016.

Future minimum payments required under the leases as of December 31, 2016, are as follows (in thousands):

Year Ending December 31:	Amount
2017	$ 6,685
2018	6,431
2019	6,624
2020	6,823
2021	7,027
Thereafter	30,335
Total minimum lease payments	$ 63,925

Letters of Credit

As of December 31, 2016 and 2015, the Company had restricted cash of $3.2 million and $0.7 million, respectively, representing letters of credit securing the Company's obligations under certain leased facilities in Cambridge, Massachusetts at 200 Sidney Street and the 610 Main Street as well as certain credit card arrangements. The letters of credit are secured by cash held in a restricted depository account. The cash deposit is recorded in restricted cash in the accompanying consolidated balance sheet as of December 31, 2016 and 2015.

Shareholder Settlement

Under the terms of a shareholder agreement existing prior to the IPO, if a U.S. common shareholder elected to file a Qualified Electing Fund ("QEF") and notified the Company of this election, the Company was required to make advance payments to the shareholder related to their individual tax liability. In September 2016, the Company formally offered an aggregate settlement of up to $2.0 million to certain U.S common shareholders in order to release the Company from any and all obligations or claims concerning and/or arising out of the Company's status as a PFIC or a Controlled Foreign Corporation (a "CFC") for any taxable year from 2013 through 2015, including for potential lack of timely notification of the Company's PFIC status (an "Annual Information Statement") for the year ended December 31, 2015.

Following the formal settlement offer in September 2016, in the fourth quarter of 2016 the Company made payments to shareholders of $2.0 million, respectively, under the terms of the accepted settlements. The obligation to make advance payments under the shareholder agreement for tax years subsequent to 2015 terminated upon the closing of the IPO.

The Company has made available a 2016 PFIC Annual Information Statement on its website for its shareholders.

Sponsored Research Agreements

The Company has engaged several research institutions to identify new delivery strategies and applications of the CRISPR/Cas9 technology. As a result of these efforts, the Company sponsored five research programs during 2016, with two of these programs continuing through 2018. In association with these agreements, the Company has committed to making payments for related research and development services of $0.7 million, and $0.1 million in 2017 and 2018, respectively.

License Agreement with Anagenesis Biotechnologies SAS

On June 7, 2016, the Company entered into a license agreement with Anagenesis Biotechnologies SAS ("Anagenesis") pursuant to which the Company received an exclusive worldwide license to Anagenesis' proprietary technology for all human based muscle diseases. Pursuant to the license agreement, the Company made a one-time upfront payment of $0.5 million to Anagenesis and is required to pay Anagenesis up to $89.0 million upon the achievement of future clinical, regulatory and sales milestones for each of the first allogeneic and autologous licensed products developed pursuant to the license agreement, as well as low single digit royalty payments on future sales of commercialized product candidates. The Company recorded the $0.5 million payment during the twelve months ended December 31, 2016 as research and development expense on the consolidated statement of operations.

Licensing and Patent Assignment Agreements

In April 2014, the Company and TRACR entered into technology license agreements with Dr. Emmanuelle Charpentier pursuant to which the Company licensed Dr. Charpentier's interest to certain intellectual property rights jointly owned by Dr. Charpentier and others to develop and commercialize products for the treatment or prevention of human diseases. See Note 9 for further details.

Litigation

Under the Charpentier license agreement, the Company licenses a U.S. patent application that is currently subject to interference proceedings declared by the Patent Trial and Appeal Board ("PTAB") of the U.S. Patent and Trademark Office. Following motions by the parties and other procedural matters, the PTAB concluded in February 2017 that the declared interference should be dismissed because the claim sets of the two parties were not directed to the same patentable invention in accordance with the PTAB's two-way test for patent interferences. See Note 17 for further details.

Under the Invention Management Agreement ("IMA") signed on December 15, 2016, the Company is obligated to share costs related to patent maintenance, defense and prosecution. For the years ended December 31, 2016, 2015 and 2014, the Company incurred $3.0 million, $1.5 million and $1.1 million, respectively in shared costs. The Company recorded accrued legal costs from the cost sharing of $2.8 million and $2.6 million as of December 31, 2016 and 2015, respectively

9. Significant Contracts

Intellectual Property Agreements

CRISPR Therapeutics AG—Charpentier License Agreement

In April 2014, the Company entered into a technology license agreement with Dr. Emmanuelle Charpentier pursuant to which the Company licensed certain intellectual property rights under joint ownership from Dr. Charpentier to develop and commercialize products for the treatment or prevention of human diseases other than hemoglobinopathies ("CRISPR—Charpentier License Agreement"). In consideration for the granting of the license, the Company paid Dr. Charpentier an upfront fee of CHF 0.1 million ($0.1 million), and agreed to pay an immaterial annual license maintenance fee if Dr. Charpentier is not otherwise engaged in a service arrangement with the Company. During the years ended December 31, 2016, 2015 and 2014, Dr. Charpentier has been in a consulting arrangement with the Company, as such, no annual payments have been made under this provision. Dr. Charpentier is entitled to receive nominal clinical milestone payments. The Company is also obligated to pay Dr. Charpentier a low single digit percentage of sublicensing payments received under any sublicense agreement with a third party. In addition, the Company is also obligated to pay to Dr. Charpentier a low single-digit percentage royalty based on annual net sales of licensed products and licensed services by the Company and its affiliates and sublicensees.

During the years ended December 31, 2016, 2015, and 2014 the Company recorded and accrued $0.5 million, $0.9 million, and $0 million, respectively, of sublicensing fees due to Dr. Emmanuelle Charpentier in research and development expense under the terms of the CRISPR—Charpentier License Agreement that was triggered by the execution of the Vertex collaboration agreement and the Bayer agreement.

TRACR Hematology Limited—Charpentier License Agreement

In April 2014, TRACR entered into a technology license agreement ("TRACR—Charpentier License Agreement") with Dr. Emmanuelle Charpentier pursuant to which TRACR licensed certain intellectual property rights under joint ownership from Dr. Charpentier to develop and commercialize products for the treatment or prevention of human diseases related to hemoglobinopathies. In consideration for the granting of the license, Dr. Charpentier is entitled to receive nominal clinical milestone payments. TRACR is also obligated to pay Dr. Charpentier a low single digit percentage of sublicensing payments received under any sublicense agreement

with a third party. In addition, TRACR is obligated to pay to Dr. Charpentier low single digit percentage royalties based on annual net sales of licensed products and licensed services by the Company and its affiliates and sublicensees.

During the years ended December 31, 2016, 2015, and 2014 the Company recorded $0, $0.1 million, and $0, respectively, of sublicensing fees due to Dr. Emmanuelle Charpentier in research and development expense under the terms of the TRACR—Charpentier License Agreement that was triggered by the execution of the Vertex collaboration agreements.

Invention Management Agreement

On December 15, 2016, we entered into a an IMA, with the University of California ("California"), the University of Vienna ("Vienna"), Dr. Charpentier, Intellia therapeutics, Inc. ("Intellia"), Caribou Biosciences, Inc. ("Caribou"), ERS Genomics Ltd., or ("ERS"), and TRACR. Under the IMA, California and Vienna retroactively consent to Dr. Charpentier's licensing of her rights to the CRISPR/Cas9 intellectual property, pursuant to the Charpentier License, to us, our wholly-owned subsidiary TRACR, and ERS, in the United States and globally. The IMA also provides retroactive consent of co-owners to sublicenses granted by us, TRACR and other licensees, prospective consent to sublicenses they may grant in future, retroactive approval of prior assignments by certain parties, and provides for, among other things, (i) good faith cooperation among the parties regarding patent maintenance, defense and prosecution, (ii) cost-sharing arrangements, and (iii) notice of and coordination in the event of third-party infringement of the subject patents and with respect to certain adverse claimants of the CRISPR/Cas9 intellectual property. Unless earlier terminated by the parties, the IMA will continue in effect until the later of the last expiration date of the patents underlying the CRISPR/Cas9 technology, or the date on which the last underlying patent application is abandoned.

Patent Assignment Agreement

In November 2014, the Company entered into a patent assignment agreement ("Patent Assignment Agreement") with Dr. Emmanuelle Charpentier, Dr. Ines Fonfara, and Vienna (collectively, the "Assignors"), pursuant to which the Company was assigned all rights, title and interest in and to certain patent rights claimed in the U.S. Patent Application No.61/905,835. In consideration for the assignment of such rights, the Assignors are entitled to receive clinical milestone payments totaling up to €0.3 million (approximately $0.4 million) in the aggregate for the first human therapeutic product. The Company is also obligated to pay to the Assignors low single digit royalties based on annual net sales of licensed products and licensed services by the Company and its affiliates and sublicensees.

During the years ended December 31, 2016, 2015, and 2014 the Company recorded $33 thousand, $0.1 million, $0, respectively, of sublicensing fees due to the Assignors in research and development expense under the terms of the Patent Assignment Agreement that was triggered by the execution of the Vertex collaboration agreement and the Bayer Agreement.

Collaboration Agreement with Vertex Pharmaceuticals, Incorporated

Summary of Agreement

On October 26, 2015, the Company entered into a strategic collaboration, option, and license agreement ("Collaboration Agreement") with Vertex, focused on the use of CRISPR's gene editing technology, known as CRISPR/Cas9, to discover and develop potential new treatments aimed at the underlying genetic causes of human disease. The collaboration will evaluate the use of CRISPR-Cas9 across multiple diseases where targets have been validated through human genetics. Vertex and CRISPR will focus their initial gene editing research on discovering treatments to address the mutations and genes known to cause and contribute to sickle cell disease, beta-thalessemia and cystic fibrosis. Vertex and CRISPR will also evaluate a specified number of other genetic targets as part of the collaboration. For up to six targets, Vertex has an exclusive option to obtain: (1) an exclusive license to commercialize CRISPR technology ("Exclusive License") or (2) a co-exclusive license with respect to hemoglobinopathy and beta-globin targets ("Co-exclusive License").

The collaborative program of research to be undertaken by the parties pursuant to the Collaboration Agreement will be conducted in accordance with a mutually agreed upon research plan which outlines each party's research and development responsibilities across the three research areas. The Company's research and development responsibilities under the research plan ("R&D Services") are related to generating genome editing reagents that modify gene targets selected by Vertex. Except with respect to the Company's obligations under the mutually agreed upon research plan, Vertex has sole responsibility, at its own costs, for the worldwide research, development, manufacturing and commercialization of products resulting from the exclusive licenses obtained.

The research collaboration will end on the earlier of the date on which Vertex has exercised six options to obtain exclusive/co-exclusive licenses with respect to a collaboration target, or the fourth anniversary of the effective date of the agreement. The research

term may be extended as mutually agreed by the parties up to nine additional months to complete any research activities under the approved research plan that are incomplete on the fourth anniversary of the effective date.

The Collaboration Agreement will be managed on an overall basis by a project leader from each of the Company and Vertex. In addition, the activities under the collaboration agreement during the research term will be governed by a joint research committee ("JRC") formed by an equal number of representatives from the Company and Vertex. Decisions by the JRC will be made by consensus of the group, however, Vertex will have final decision-making authority in the event of disagreement, provided it is in good faith and not contrary to any explicit clause of the agreement.

In connection with the agreement, Vertex made a nonrefundable upfront payment of $75.0 million. In addition, Vertex will fund all of the discovery activities conducted pursuant to the agreement. For potential hemoglobinopathy treatments, including treatments for sickle cell disease, the Company and Vertex will share equally all research and development costs and worldwide revenues. For other targets that Vertex elects to license, Vertex would lead all development and global commercialization activities. For each of up to six targets that Vertex elects to license, other than hemoglobinopathy and beta-globin targets, the Company has the potential to receive up to $420.0 million in development, regulatory and commercial milestones and royalties on net product sale.

Vertex is entitled to terminate the Collaboration Agreement as a whole, or terminate the Collaboration Agreement in part with respect to a particular collaboration program, for convenience by providing the Company 90 days' written notice of such termination; provided, however, that if any termination applies to a product for which Vertex has received marketing approval, Vertex will provide CRISPR no less than 270 days' notice of such termination. If Vertex is in material breach of this Collaboration Agreement, the Company has the right to terminate the Collaboration Agreement in full at its discretion 90 days after delivery of written notice to Vertex.

The Company evaluated the Collaboration Agreement in accordance with the provisions of ASC 605-25. The Company's arrangement with Vertex contains the following initial deliverables: (i) a non-exclusive research license; (ii) the option to obtain an exclusive license for up to six Collaboration Targets; (iii) the option to obtain a co-exclusive license for hemoglobinopathy or beta-globin targets (which would be included within the maximum number of the aforementioned six collaboration targets); (iv) R&D Services; and (v) JRC participation.

Management considered whether any of these deliverables could be considered separate units of accounting. Regarding the non-exclusive research license, the Company concluded that it does not have stand-alone value separate from the option to exercise the exclusive or co-exclusive license since Vertex would not benefit from acquiring a research license without the ability to obtain the license to commercialize the results of that research. As a result, the Company concluded that the research license should be combined with those options.

Regarding the R&D Services, the Company concluded that there are other vendors in the market that could perform the related services. As such the Company concluded the R&D Services represent a separate unit of accounting.

Regarding the JRC obligations, the Company concluded that the JRC obligations deliverable has standalone value from the option to license because the services could be performed by an outside party. As such the Company concluded the JRC obligations represent a separate unit of accounting.

As a result, management concluded that there are four units of accounting at the inception of the agreement: (i) a combined unit of accounting representing the non-exclusive research license, and the option for up to six exclusive licenses to develop and commercialize the collaboration targets as these options do not have stand- alone value; (ii) a combined unit of accounting representing the non-exclusive research license, and the option for a co-exclusive license (subject to the aforementioned six license limit) to develop and commercialize the hemoglobinopathy or beta-globin targets as these options do not have stand-alone value; (iii) the performance of R&D Services; and (iv) the participation in the JRC.

The Company has determined that neither VSOE of selling price nor TPE of selling price is available for any of the units of accounting identified at inception of the arrangement. Accordingly, the selling price of each unit of accounting was determined based on the Company's BESP. The Company developed the BESP for all of the units of accounting included in the collaboration agreement with the objective of determining the price at which it would sell such an item if it were to be sold regularly on a standalone basis.

The Company developed the BESP for the R&D Services and the JRC participation primarily based on the nature of the services to be performed and estimates of the associated effort and cost of the services, adjusted for a reasonable profit margin that would be expected to be realized under similar contracts. The Company's BESP for the R&D Services was $26.7 million. The Company's BESP for the JRC participation services was de minimis based on an estimate of time spent on preparation, participation, review and travel for the meetings.

The Company's BESP for each combined unit of the non-exclusive research license and the option for an exclusive license to develop and commercialize a single collaboration target is $37.7 million. As the Company expects Vertex to exercise five of these options, the total BESP is $188.5 million. BESP for this item was determined based on probability and present value adjusted cash flows from the royalties and milestones outlined in the Collaboration Agreement. BESP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

The Company's BESP for a non-exclusive research license and the option for a co-exclusive license to develop and commercialize a single hemoglobinopathy or beta-globin collaboration target is $12.5 million. As the Company expects Vertex to exercise one of these options, the total BESP is $12.5 million. BESP for this item was determined based on probability and present value adjusted cash flows from the equal sharing of project worldwide net profit or net loss. BESP reflects the level of risk and expected probability of success inherent in the nature of the associated research area.

Allocable arrangement consideration at inception is comprised of: (i) the up-front payment of $75.0 million, (ii) the estimated R&D services of $26.7 million and (iii) payments related to the estimated exercise of options on future exclusive licenses for five targets of $50.0 million. The aggregate allocable arrangement consideration of $151.7 million was allocated among the separate units of accounting using the relative selling price method as follows: (i) R&D Services: $17.8 million, (ii) non-exclusive research license, and the option for an Exclusive License to develop and commercialize the five collaboration targets: $125.5 million, (iii) non-exclusive research license, and the option for one Co-exclusive License to develop and commercialize one hematology target: $8.4 million.

The amount allocated to R&D Services will be recognized as the R&D Services are performed. The Company will recognize as license revenue an equal amount of the total arrangement consideration allocated to the exclusive licenses as each individual license is delivered to Vertex upon Vertex's exercise of its options to such licenses. The Company will recognize $8.4 million as license revenue when the Co-exclusive License is delivered to Vertex upon Vertex's exercise of its options to such license.

The Company has evaluated all of the milestones that may be received in connection with the Collaboration Agreement. In evaluating if a milestone is substantive, the Company assesses whether: (i) the consideration is commensurate with either the Company's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the Company's performance to achieve the milestone, (ii) the consideration relates solely to past performance, and (iii) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. The Company notes that the $10.0 million due upon the exercise of each option for an Exclusive License was determined to be part of the fixed and determinable consideration allocable at contract inception and is not subject to milestone method accounting.

The first potential milestone the Company will be entitled to receive is the $10.0 million milestone due upon the filing of an Investigational New Drug Application ("IND") for a selected Exclusive License. As the first developmental milestone of the agreement relates to the filing of an IND, the Company has considered it to be substantive. Accordingly, such amounts will be recognized as revenue in full in the period in which the associated milestone is achieved, assuming all other revenue recognition criteria are met. There are no other substantive milestones. As such the total amount of substantive milestones subject to milestone method accounting treatment is $10.0 million for each selected Exclusive License.

The remaining milestones are predominately related to the development and commercialization of a product resulting from the arrangement and are payable with respect to each selected Exclusive License. Each milestone is payable only once per collaboration target, regardless of the number of products directed to such collaboration target that achieve the relevant milestone event. There are nine remaining clinical development and regulatory approval milestones which may trigger proceeds of up to $90.0 million and $235.0 million, respectively, for each selected Exclusive License, and two commercial milestones which may trigger proceeds of up to $75.0 million for each selected Exclusive License (which, when combined with the $10.0 million due upon exercise of the exclusive option and the $10.0 million development milestone associated with an IND, total $420.0 million for each selected Exclusive License), as follows:

Developmental Milestone Events

1. Initiation of the first Clinical Trial of a Product
2. Establishment of POC for a Product
3. Initiation of the first Phase 3 Clinical Trial of a Product
4. Acceptance of Approval Application by the FDA for a Product
5. Acceptance of Approval Application by the EMA for a Product

6. Acceptance of Approval Application by a Regulatory Authority in Japan for a Product
7. Marketing Approval in the US for a Product
8. Marketing Approval in the EU for a Product
9. Marketing Approval in Japan for a Product

Commercial Milestone Events

1. Annual Net Sales for Products with respect to a Collaboration Target exceed $500 million
2. Annual Net Sales for Products with respect to a Collaboration Target exceed $1.0 billion

After Vertex has exercised an Exclusive License option, Vertex will be solely responsible for all research, development, manufacturing, and commercialization of licensed agents and products for the relevant target. As the Company's involvement in this process is limited to observer status, management determined that milestones are not considered substantive because they do not relate solely to the past performance of the Company. Upon the achievement of a milestone, management will evaluate whether the triggering event occurs during or after the research term. If the triggering event occurs during the research term, management has elected to treat the milestone similar to an up-front payment. In these cases, if and when any of these milestones are received, the amount will be included in the overall arrangement consideration and allocated to the remaining identified deliverables. To the extent all deliverables have been satisfied, any additional consideration allocated to them could be immediately recognized. If the triggering event occurs after the research term, the Company will recognize the associated revenue in the period in which the event occurs. The Company will recognize royalty revenue in the period of sale of the related product(s), based on the underlying contract terms, provided that the reported sales are reliably measurable and the Company has no remaining performance obligations, assuming all other revenue recognition criteria are met.

During the year ended December 31, 2016, 2015, and 2014, the Company recognized $4.0 million, $0.2 million, and $0 million of revenue with respect to the collaboration with Vertex. Research and development expense incurred by the Company in relation to its performance under the collaboration agreement for the years ended December 31, 2016 and 2015 was $7.0 million and $0.3 million, respectively. As of December 31, 2016 and 2015, there is $77.1 million and $75.1 million of non-current deferred revenue related to the Company's collaboration with Vertex, respectively.

Joint Venture with Bayer Healthcare LLC

On December 19, 2015, the Company entered into an agreement to establish a joint venture ("Bayer Joint Venture") to research the development of new therapeutics to cure blood disorders, blindness, and congenital heart disease. On February 12, 2016, the Company and Bayer completed the formation of the joint venture entity, Casebia, a limited liability partnership formed in the United Kingdom. Bayer and the Company each received a 50% equity interest in the entity in exchange for their contributions to the entity. The Company contributed $0.1 million in cash and licensed its proprietary CRISPR/Cas9 gene editing technology and intellectual property for selected disease indications. Bayer contributed its protein engineering expertise and relevant disease know-how.

Bayer will provide up to $300.0 million in research and development funding to Casebia over the first five years, subject to certain conditions, of which the first $45.0 million was contributed upon formation in the first quarter of 2016. Under the joint venture agreement, the Company has no obligation to provide any additional funding and the Company's ownership interest will not be diluted from future contributions from Bayer. The activities of Casebia are controlled by a management board under the joint control of the Company and Bayer. As Casebia is jointly controlled by the Company and Bayer, the Company accounts for its 50% interest using the equity method of accounting.

Under the agreement, Casebia will pay the Company up to $35.0 million in exchange for a worldwide, exclusive license to commercialize the Company's CRISPR/Cas9 technology specifically for the indications designated by Casebia. In March 2016, the Company received a non-refundable up-front payment of $20.0 million as a technology access fee. The remaining $15.0 million was paid on December 22, 2016 following delivery of the necessary consents from patent holders of the Company's intellectual property. There are no milestone, royalties or other payments due to the Company under this aspect of the agreement. The Company determined that the contribution of the CRISRP/Cas9 technology by license to Casebia did not meet the definition of a business under ASC 805.

The Company will also provide to Casebia compensated research and development services through a separate agreement.

Concurrent with the execution of the Bayer Joint Venture agreement, the Company also entered into the Bayer Convertible Loan for $35.0 million.

As the Bayer Joint Venture (including the CRISPR/Cas9 technology license and the research and development services) and the Bayer Convertible Loan were executed at the same time, the Company determined that they should be evaluated as one multiple-element arrangement. Additionally, the Company also determined that ASC 845, *Nonmonetary Transactions* ("ASC 845") did not apply to this arrangement given the Company's significant continuing involvement with Casebia and the amount of cash involved in the arrangement. As a result, the Company analogized to ASC 605-25 in allocating the relative fair value of the consideration received to the different elements of the arrangement.

The Company allocated the fair value of the consideration received using a relative fair value allocation. The allocable arrangement consideration included (i) the total cash payment by Casebia for the technology access fee, net of the Company's $0.1 million contribution, of $34.9 million, (ii) the fair value of the equity interest in the Joint Venture of $36.4 million, (iii) the $35.0 million received from the issuance of the Convertible Debt, and (iv) $6.3 million of estimated cash consideration to be received under the research and development service arrangement, accumulating to $112.6 million.

The Company identified the following elements under the transaction:

(i) Combined element of an exclusive, worldwide, royalty free, license to the CRISPR/Cas9 technology specifically for the indications designated by Casebia, and delivery of the consents of the assignors of the underlying patents to the technology to develop, manufacture, and commercialize licensed products under that license

(ii) Research and development services, and

(iii) The issuance of the Bayer Convertible Loan.

The Company determined the fair value of the license was $71.4 million based on the consideration paid and the fair value of the 50% interest in Casebia, which was determined utilizing discounted cash flows based on reasonable estimates and assumptions of cash flows expected from Casebia. The fair value of the separate research and development services was determined to be $6.3 million. The fair value of the Bayer Convertible Loan was determined to be $24.5 million, based on the fair value of the underlying preferred shares that were exchanged as part of the immediate conversion. Using a relative fair value allocation, the Company allocated the aggregate arrangement consideration paid as follows:

(i) $63.6 million was allocated to the license and patent holder consent combined element

(ii) $0.6 million was allocated to the future research and development services

(iii) $27.0 million was allocated to the Bayer Convertible Loan

The difference between combined above amounts of $91.2 million and the total allocable arrangement consideration of $112.6 million is due to allocable arrangement consideration associated with the $6.3 million of estimated cash consideration to be received under the research and development service arrangement and the remaining $15.0 million of the license fee paid upon the delivery of the consent from the patent holders of the Company's intellectual property.

Following delivery of the patent holders' consent, which occurred on December 17, 2016, the combined amount attributed to the license and patent holder consent element and the remaining $15.0 million license fee, which amount to $78.6 million, was recognized as other income for the year ended December 31, 2016. The Company had determined that the license and patent holder consent combined element did not meet the definition of revenue because the licensing of its technology in connection with the formation of a joint venture is not part of the Company's major ongoing or central operations.

As the amount allocated to the Bayer Convertible Loan represents an $8.0 million discount to its $35.0 million face value, the Company recognized interest expense during the twelve months ended December 31, 2016 equal to the discount. The Convertible Loan automatically converted into Series B preferred shares on its January 29, 2016 maturity date.

During 2016, the Company recorded an equity method investment of $36.5 million equal to the fair value of the Company's interest in Casebia (which was included in the allocable arrangement consideration described above). Following delivery of the patent holders consent element and realization of the described gain allocated to the license and patent holder consent combined element, the Company recorded unrealized equity method losses up to the remaining amount of the $36.5 million investment.

During the year ended December 31, 2016, the Company recognized $1.2 million, of revenue with respect to the collaboration with Casebia. Research and development expense incurred by the Company in relation to its performance under the agreement for the year ended December 31, 2016 was $1.2 million. As of December 31, 2016, there is $0.5 million of non-current deferred revenue related to the Company's collaboration with Casebia, respectively. Unrecognized equity method losses in excess of the Company's investment in Casebia totaled $4.0 million as of and for the year ended December 31, 2016. During 2016, the Company recorded $0.2 million of stock-based compensation expense related to Casebia employees.

Total operating expenses, and net loss of Casebia for the twelve months ended December 31, 2016 was $80.8 million, which included research and development expenses equal to $77.4 million for the fair value of the CRISPR license acquired.

Subscription Agreement with Bayer Global Investments B.V.

On December 19, 2015, the Company entered into a subscription agreement, ("Subscription Agreement"), with Bayer BV. Pursuant to the Subscription Agreement, Bayer BV was given the option, at its election, to purchase $35.0 million of the Company's Common Shares in a private placement concurrent with the Company's IPO at a per share price equal to the public offering price, see Note 16 for further details.

10. Redeemable Convertible Preferred Shares

Upon the closing of the Company's IPO on October 24, 2016, all outstanding Preferred Shares of the Company were automatically converted into 27,135,884 Common Shares on a one-for-one basis. As of December 31, 2016, the Company had no Preferred Stock authorized, issued, or outstanding.

As of December 31, 2015, the Company had 18,837,024 registered Preferred Shares issued and outstanding in share capital, which was comprised of (i) 440,001 Series A-1 Preferred Shares CHF 0.03 par value per share; (ii) 3,120,001 Series A-2 Preferred Shares, CHF 0.03 par value per share; (iii) 10,758,006 Series A-3 Preferred Shares, CHF 0.03 par value per share; and, (iv) 4,519,016 Series B Preferred Shares, CHF 0.03 par value per share, (collectively, the "Preferred Shares") .

The Company's redeemable convertible preferred shares were classified as temporary or mezzanine equity on the accompanying consolidated balance sheets in accordance with authoritative guidance for the classification and measurement of redeemable securities as the Preferred Shares are contingently redeemable at the option of the holders.

In October 2013, the Company issued 440,001 Series A-1 Preferred Shares for CHF 1.14 ($1.28) per share, resulting in gross proceeds of CHF 0.5 million ($0.6 million). Under the terms of the Series A-1 Preferred Shares Investment Agreement, the holders had the right to purchase an additional 1,315,790 Series A-1 Preferred Shares at CHF 1.14 ($1.28) per share (the "Series A-1 Tranche Rights") contingent upon two or more shareholders holding Series A-1 Preferred Shares. These rights were not legally detachable. The Series A-1 Tranche Rights were evaluated under ASC 480 and ASC 815 and it was determined that they did not meet the requirements for separate accounting from the initial issuance of Series A-1 Preferred Shares. In connection with the issuance of the Series A-1 Preferred Shares, the Company also issued 335,000 Common Shares to the Series A Preferred Shares investors. The Company recorded the difference of $0.1 million between the fair value of the Common Shares issued and the price paid by the investors as an issuance cost discount to the Series A-1 Preferred Shares upon issuance.

In April 2014, the Company issued 3,120,001 Series A-2 Preferred Shares in exchange for CHF 3.05 ($3.47) per share of such amount CHF 1.45 ($1.65) per share was received upon issuance resulting in gross proceeds of CHF 4.5 million ($5.1 million) and the balance of CHF 1.60 ($1.82) per share was called in February 2015 by the Board of Directors of the Company resulting in additional gross proceeds of CHF 5.0 million ($5.3 million).

In connection with the issuance of the Series A-2 Preferred Shares, the Series A-1 Tranche Rights were terminated without exercise in April 2014. The Company's policy requires the evaluation of amendments to preferred shares qualitatively to determine whether they are considered a modification or extinguishment. Based on this approach, the amendment to the terms of the Series A-1 Preferred Shares was considered an extinguishment due to the significance of the modifications to the substantive contractual terms of the Series A-1 Preferred Shares. Accordingly, the Company recorded a loss of $0.7 million on the Series A-1 Preferred Shares within additional paid-in capital equal to the difference between the fair value of the Series A-1 Preferred Shares of $1.2 million and the carrying amount of the Series A-1 Preferred Shares of $0.4 million upon extinguishment. The loss on extinguishment is reflected in the calculation of net loss available to common stockholders in accordance with FASB ASC Topic 260, *Earnings per Share* ("ASC 260").

In April 2015, the Company issued 10,758,006 Series A-3 Preferred Shares in exchange for $4.24 per share whereby $2.12 per share was received upon issuance, resulting in gross proceeds of $22.8 million and the balance of $2.12 per share was due upon meeting certain milestones. As of December 31, 2015, none of the milestones had occurred and the Company had an outstanding subscription receivable of $22.8 million related to the Series A-3 Preferred Shares. In connection with the issuance of the Series A-3 Preferred Shares, the Company amended the dividend and conversion terms of the Series A-1 and Series A-2 Preferred Shares. The Company's policy requires the evaluation of amendments to equity classified preferred shares qualitatively to determine whether they are considered a modification or extinguishment. Based on this approach, the amendment to the terms of the Series A-1 and A-2 Preferred Shares was considered a modification and as a result, there was no adjustment to the carrying value of the Series A-1 and A-2 Preferred Shares. The balance of the Series A-3 Preferred Share subscription receivable of $2.12 per share was called on May 5, 2016 by the Board of Directors and gross proceeds of $22.8 million were received by May 27, 2016.

In May 2015, the Company issued 4,519,016 Series B Preferred Shares in exchange for CHF 6.20 ($6.74) per share resulting in gross proceeds of CHF 28.0 million ($30.5 million).

In January 2016, the Company issued 5,464,608 Series B Preferred Shares upon conversion of $38.4 million of Vertex Convertible Loans plus accrued interest and $35.0 million of Bayer Convertible Loans at a conversion price of $13.43 per share.

In June 2016, the Company issued 2,834,252 Series B Preferred Shares in exchange for $13.43 per share resulting in gross proceeds of $38.1 million.

11. Share Capital

The Company had 40,253,674 and 5,528,079 registered Common Shares as of December 31, 2016 and 2015, respectively, with a par value of CHF 0.03 per share. Included in the registered Common Shares as of December 31, 2016 is 89,367 shares of unvested restricted stock award and 444,873 treasury shares, which are legally outstanding, but are not considered outstanding for accounting purposes.

Conditional Capital Reserved for Future Issuance

The Company had the following conditional capital reserved for future issuance:

		As of December 31,	
Type of Share Capital	**Conditional Capital**	**2016**	**2015**
Common Shares	Charpentier Call Option	—	328,017
Common Shares	Unvested unissued restricted stock	166,667	142,794
Common Shares	Outstanding stock options	4,535,371	1,939,986
Common Shares	Reserved for future issuance under stock option plans	5,290,643	33,567
Common Shares	Shares available for bonds and similar debt instruments	4,919,700	—
Common Shares	Shares available for employee purchase plans	413,226	—
	Total	15,325,607	2,444,364

Common Share Issuances

In October 2016, the Company completed an IPO whereby the Company sold 4,429,311 of its Common Shares, inclusive of 429,311 Common Shares sold by the Company pursuant to the partial exercise of an overallotment option granted to the underwriters in connection with the offering. Concurrent with the IPO, the Company issued and sold 2,500,000 Common Shares to Bayer BV, in a private placement. Additionally, the Company issued and subsequently reacquired the unexercised overallotment Common Shares of 170,689 at no cost, which are held in treasury.

In March 2015, the Company entered into an agreement to acquire 82.1% of the ordinary share capital of TRACR in a share exchange transaction. In connection with this share exchange transaction, the Company issued 852,846 Common Shares to two founders of TRACR, 459,217 Common Shares to Fay Corp. and 656,031 restricted Common Shares to certain employee and non-employee advisors of TRACR. If the holders of any restricted common shares terminates the service relationship the unvested shares are subject to a right of repurchase at an escalating purchase price. If any of these holders of restricted Common Shares are terminated, in certain circumstances, the vested and unvested shares are subject to a right of repurchase at the shareholder's original purchase price. The Company recorded equity-based compensation expense in April 2015 for the incremental value received by the holders in exchange for the vested TRACR shares as of the exchange date. The Company is also recognizing additional equity-based compensation expense for the exchange of TRACR restricted share awards which will continue to vest over a remaining term in the form of CRISPR restricted share awards. See Note 12 for further details of equity-based compensation related to this share exchange transaction.

In April 2014, in conjunction with the sale of its Series A-2 Preferred Shares, the Company and its founders agreed to transfer 729,800 Founders' Shares to several non-employees. The shares transferred were subject to service-based vesting conditions. If the holder of any restricted Common Shares terminates the service relationship, the unvested shares are subject to a right of repurchase at an escalating purchase price. Both vested and unvested shares are subject to a right of repurchase at the original purchase price upon certain triggering events such as termination for cause, material breach of agreement, and insolvency of the holder. In addition, the founders and an investor also agreed to transfer 1,192,585 fully vested Common Shares to Fay Corp. The Company recorded equity-based compensation expense for the Founders Shares and the Common Shares issued with vesting restrictions from the founders and Fay Corp. See Note 12 for further details of equity-based compensation related to these transfers.

The Common Shares have the following characteristics:

Voting Rights

The holders of Common Shares are entitled to one vote for each Common Share held at all meetings of shareholders and written actions in lieu of meetings.

Dividends

The holders of Common Shares are entitled to receive dividends, if and when declared by the Board of Directors. As of December 31, 2016, no dividends have been declared or paid since the Company's inception.

Liquidation

After payment to the holders of Preferred Shares of their liquidation preferences, 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.

12. Equity-based Compensation

Option and Grant Plans

In July 2016, the shareholders approved the 2016 Share Option and Incentive Plan (the "2016 Plan") and in April 2015, the shareholders approved the 2015 option and grant plan (the "2015 Plan" collectively the "Plans"). Subsequent to the IPO, no further options shall be granted under the 2015 Plan. The Plans provide for the issuance of equity awards in the form of restricted shares, options to purchase Common Shares which may constitute incentive stock options ("ISOs") or non-statutory stock options ("NSOs"), unrestricted stock unit grants, and qualified performance-based awards to eligible employees, officers, directors, non-employee consultants, and other key personnel. Terms of the equity awards, including vesting requirements, are determined by the Board, subject to the provisions of the Plans. Options granted by the Company typically vest over four years and have a contractual life of ten years. During the years ended December 31, 2016, 2015 and 2014, the Company also issued outstanding Common Shares previously held by Founders and Fay Corp. to employees and non-employees as equity-based compensation ("Founder Awards"), which are subject to repurchase by the Company upon termination of the holder's service relationship with the Company as well as upon certain triggering events such as termination for cause, material breach of agreement and insolvency of the holder that generally lapse over a requisite service period of four years.

Equity-Based Compensation Expense

The Company uses the straight-line attribution method to recognize stock-based compensation expense for stock options and restricted stock awards. Stock options and restricted stock generally vests over four years with 25% vesting on the first anniversary, and the remaining vesting monthly thereafter. The following table presents stock-based compensation expense in the Company's Consolidated Statements of Operations:

	Year Ended December 31,		
	2016	2015	2014
Research and development	$ 4,848	$ 1,924	$ 487
General and administrative	5,844	1,760	208
Loss from equity method investment	152	—	—
Total	$ 10,844	$ 3,684	$ 695

Grant- Date Fair Value

There were no stock options granted prior to 2015. The Company estimated the fair value of each employee and non-employee stock option award on the grant date using the Black-Scholes option-pricing model based on the following assumptions:

	Year Ended December 31	
	2016	2015
Employees:		
Options granted	2,411,240	1,913,319
Weighted - average exercise price	$ 12.19	$ 2.32
Weighted-average grant date fair value	$ 8.47	$ 3.11
Assumptions:		
Weighted-average expected volatility	81.0%	76.4%
Expected term (in years)	6.0	6.0
Weighted-average risk free interest rate	1.4%	1.7%
Expected dividend yield	0.0%	0.0%
Non employees:		
Options granted	215,710	26,667
Weighted- average exercise price	$ 19.54	$ 1.85
Weighted- average grant date fair value	$ 17.38	$ 5.05
Assumptions:		
Weighted average expected volatility	88.2%	84.1%
Expected term (in years)	10.0	10.0
Weighted-average risk free interest rate	2.4%	2.2%
Expected dividend yield	0.0%	0.0%

The fair value of the restricted stock awards was determined based on the fair value of Common Stock on the grant date. Non-employee stock options and restricted stock awards are marked-to-market at each reporting period.

Share Based Payment Activity

Stock Options

The following table summarizes stock option activity for employees and non-employees during the year ended December 31, 2016 (intrinsic value in thousands):

	Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at December 31, 2015	1,939,986	$ 2.31	9.7	$ 6,688
Granted	2,626,950	$ 12.79		
Exercised	(18,900)	1.81		$ 216
Cancelled or forfeited	(12,665)	4.98		
Outstanding at December 31, 2016	4,535,371	$ 8.38	9.1	$ 53,975
Exercisable at December 31, 2016	960,867	$ 3.24	8.8	$ 16,361
Vested or expected to vest at December 31, 2016 (1)	4,169,347	$ 8.23	9.1	$ 50,155

(1) This represents the number of vested stock options as of December 31, 2016 plus the unvested outstanding options at December 31, 2016 expected to vest in the future, adjusted for estimated forfeitures.

The total unrecognized compensation cost for employee and non-employee stock options is adjusted for estimated forfeitures. As of December 31, 2016, the Company expects to recognize total unrecognized compensation cost related to stock options of $23.4 million over a remaining weighted-average period of 3.3 years.

During 2016 and 2015, the Company granted options to purchase 123,333 and 261,389 Common Shares, respectively, subject to performance-based vesting conditions. As of December 31, 2016, options to purchase 262,538 Common Shares subject to performance-based vesting conditions were vested, as performance conditions were achieved, and options to purchase 12,500 Common Shares subject to performance-based vesting conditions were deemed probable of vesting. In addition, 686,665 options to purchase Common Shares, subject to service and performance-based vesting conditions, satisfied the performance conditions upon the Company's IPO on October 18, 2016, and will continue to vest over their requisite service periods.

Restricted Stock

The following table summarizes restricted stock activity for employees and non-employees during the year ended December 31, 2016:

	Reflected as outstanding upon vesting	Reflected as outstanding upon grant date	Total	Weighted-Average Grant Date Fair Value
Unvested restricted Common Stock at December 31, 2015	142,794	1,485,244	1,628,038	$ 4.35
Vested	(53,427)	(834,388)	(887,815)	4.78
Unvested restricted Common Stock at December 31, 2016	89,367	650,856	740,223	$ 3.84

During the years ended December 31, 2016 and 2015, the total fair value of restricted stock vested was $9.9 million, $2.3 million, respectively. At December 31, 2016, total unrecognized compensation expense related to unvested restricted stock was $7.2 million which the Company expects to recognize over a remaining weighted-average period of 1.4 years.

During 2016 and 2015, the Company granted 0 and 50,000 restricted Common Shares, respectively, subject to performance-based vesting conditions. As of December 31, 2016 and 2015, 50,000 and 0 restricted Common Shares subject to performance-based vesting conditions were vested, respectively. As of December 31, 2015, there were 15,000 restricted Common Shares subject to performance-based vesting conditions deemed probable of vesting.

During the year ended December 31, 2016, the Company and Fay Corp. transferred 290,400 Common Shares to a Founder, 268,093 of which are subject to vesting conditions with a weighted average grant date fair value of $12.65 per share. The unvested Common Shares are subject to repurchase by the Company upon termination of the holder's service relationship with the Company as well as upon certain triggering events such as termination for cause, material breach of agreement and insolvency of the holder. The Company recognized expense related to the Common Shares transferred to the Founder of $2.6 million during the year ended December 31, 2016. As of December 31, 2016, Fay Corp. no longer held outstanding Common Shares of the Company.

13. 401(k) Savings Plan

The Company established a defined-contribution savings plan under Section 401(k) of the Internal Revenue Code (the "401(k) Plan") in November 2016. The 401(k) Plan covers all employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pretax basis. The Company contributed $0.1 million to the 401(k) Plan for the year ended December 31, 2016.

14. 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. For the years ended December 31, 2016, 2015 and 2014, the loss before provision for income taxes consist of the following (in thousands):

	Year ended December 31,		
	2016	2015	2014
Domestic	$ 3,322	$ 593	$ —
Foreign	(26,040)	(26,414)	(6,863)
Total	$ (22,718)	$ (25,821)	$ (6,863)

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

	Year ended December 31,		
	2016	2015	2014
Current income taxes:			
Federal	$ (649)	$ (23)	$ —
State	11	(12)	—
Foreign	17	(26)	(11)
Total current income taxes	(621)	(61)	(11)
Deferred income taxes:			
Federal	30	(37)	—
State	105	65	—
Foreign	2	26	74
Total deferred income taxes	137	54	74
Total income tax (provision) benefit	$ (484)	$ (7)	$ 63

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, 2016, 2015 and 2014 is as follows:

	Year ended December 31,		
	2016	2015	2014
Income tax expense at statutory rate	10.3%	10.3%	10.3%
State income tax, net of federal benefit	1.3%	0.1%	0.0%
Nondeductible expenses	1.6%	0.0%	0.0%
Foreign rate differential	(3.3%)	(1.4%)	1.8%
Statutory to US GAAP permanent differences	6.6%	0.0%	0.0%
Stock-based compensation	(4.9%)	(1.4%)	(1.1%)
Research credits	3.1%	0.6%	0.0%
Change in valuation allowance	(16.8%)	(8.2%)	(10.1%)
Effective income tax rate	(2.1%)	0.0%	0.9%

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):

	Year ended December 31,	
	2016	2015
Deferred tax assets:		
Net operating loss carryforwards	$ 3,934	$ 2,600
Accruals and reserves	791	189
Deferred Rent	5,228	—
Other deferred tax assets	7	72
Deferred revenue	2,525	406
Research credit	425	104
Total deferred tax assets	12,910	3,371
Less valuation allowance	(6,770)	(2,892)
Net deferred tax assets	6,140	479
Deferred tax liabilities:		
Depreciation	(5,909)	(321)
Intangible assets	(68)	(80)
Other deferred tax liabilities	—	(53)
Total deferred tax liabilities	(5,977)	(454)
Long term deferred taxes	$ 163	$ 25

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 operating losses in its non-U.S. jurisdictions, the Company has concluded that it is more-likely-than-not that the benefit of its non-U.S. deferred tax assets will not be realized. Accordingly, the Company has provided a full valuation allowance against its net deferred tax assets in Switzerland, and in the UK for its TRACR subsidiary, as of December 31, 2016 and 2015. The valuation allowance increased by $3.9 million during 2016, which is primarily attributable to losses in Switzerland. Additionally, the Company has established a valuation allowance for certain U.S. deferred tax assets.

As of December 31, 2016, the Company had available non-U.S. net operating loss carryforwards of $41.7 million which begin to expire in 2020. As of December 31, 2016, the Company has U.S. domestic state research and development credit carryforwards of $0.2 million which begin to expire in 2031.

As of December 31, 2016, the Company has U.S. domestic federal research and development credit carryforwards of $0.3 million which expire in 2036.

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, 2016 the Company had gross unrecognized tax benefits of $0.2 million of which $0.1 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, 2016, 2015 and 2014, 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):

	Year ended December 31,		
	2016	2015	2014
Balance at beginning of year	$ 49	$ —	$ —
Increases for tax positions taken during current period	134	49	—
Increases for tax positions taken in prior periods	—	—	—
Decreases for tax positions taken during current period	—	—	—
Decreases for tax positions taken in prior periods	(20)	—	—
Balance at end of year	$ 163	$ 49	$ —

The Company files income tax returns in the U.S. federal jurisdiction, Massachusetts, and certain non-U.S. jurisdictions. The Company is subject to U.S. federal, Massachusetts, and non-U.S. income tax examinations by authorities for all tax years.

15. Selected Quarterly Financial Data (Unaudited)

Prior to its IPO on October 18, 2016, the Company had outstanding participating Preferred Shares. During the fourth quarter of the year ended December 31, 2016, the Company had net income, although for the full year the Company had a net loss. Accordingly, the Company used the two-class method to calculate net income per share for the fourth quarter of 2016. For purposes of calculating basic net income per share for the fourth quarter of 2016, the Company excluded from the numerator $3.1 million of net income attributable to participating securities. The Company calculated diluted net income per share under both the if-converted method and the two-class method and concluded that the two-class method was more dilutive than the if-converted method. Accordingly, the two-class income allocations were reapplied after taking into account the dilutive effect of non-participating securities. This resulted in net income of $3.1 million being allocated to the participating securities and excluded from the numerator of the Common Stock dilutive net income per share calculation.

	2016			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter (1)
Collaboration revenue	$ 476	$ 795	$ 1,549	$ 2,344
Total operating expenses	12,128	17,353	16,159	27,654
Loss from operations	(11,652)	(16,558)	(14,610)	(25,310)
Net (loss) income	(8,442)	(17,164)	(14,694)	17,098
Net (loss) income attributable to common shareholders	(8,439)	(17,157)	(14,680)	17,099
Net (loss) income per share attributable to common shareholders:				
Basic	$ (1.53)	$ (3.15)	$ (2.77)	$ 0.43
Diluted	$ (1.53)	$ (3.15)	$ (2.77)	$ 0.40
Weighted-average common shares outstanding used in net (loss) income per share attributable to common shareholders:				
Basic	5,528,079	5,448,855	5,292,348	32,987,335
Diluted	5,528,079	5,448,855	5,292,348	34,989,218

	2015			
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Collaboration revenue	$ —	$ —	$ —	$ 247
Total operating expenses	3,736	3,625	6,202	12,413
Loss from operations	(3,736)	(3,625)	(6,202)	(12,166)
Net loss	(3,522)	(3,666)	(6,354)	(12,286)
Net loss attributable to common shareholders	$ (3,237)	$ (3,643)	$ (6,353)	$ (12,270)
Net loss per share applicable to common shareholders- basic and diluted	$ (0.91)	$ (0.80)	$ (1.15)	$ (2.22)
Weighted-average common shares outstanding used in net loss per share attributable to common shareholders - basic and diluted	3,560,000	4,538,595	5,528,079	5,528,079

(1) During the fourth quarter the Company recorded an immaterial correction of an error of $1.2 million for rent expense related to the three months ended September 30, 2016. The Company determined that these errors are not material to the respective interim financial statements.

16. Related Party Transactions

We had the following transactions with related parties during the period:

In connection with the Series A-3 Preferred Share financing, the Company paid $0.2 million on behalf of investors for legal and consulting costs incurred for the preparation and completion of the transaction.

The Company is a party to intellectual property license agreements with Dr. Charpentier. In addition, Dr. Charpentier is a consultant to the Company. For the year ended December 31, 2016 and 2015, the Company paid Dr. Charpentier a total of $1.0 million and $34 thousand, respectively, in consulting, licensing and other fees. As of December 31, 2016 and 2015, the Company owed Dr. Charpentier approximately $0.5 million, and $1.0 million, respectively, of additional fees primarily related to the Vertex Collaboration Agreement and Bayer Joint Venture Agreement.

During the year ended December 31, 2016, the Company formed a joint venture with Bayer. As a part of the agreement to form the joint venture, the Company also issued a $35.0 million convertible loan to Bayer, which converted into Series B preferred stock and ultimately common stock upon the IPO. Bayer also purchased 2,500,000 common shares through a private placement of $35 million during 2016. During the year ended December 31, 2016 and 2015, the Company recognized $1.2 million and $0 million, respectively, related to the performance of R&D services for Casebia, the Company's joint venture with Bayer. See Note 9 for further detail.

17. Subsequent Events

Under the Charpentier license agreement, the Company licenses a U.S. patent application that is currently subject to interference proceedings declared by the PTAB of the U.S. Patent and Trademark Office. Following motions by the parties and other procedural matters, the PTAB concluded in February 2017 that the declared interference should be dismissed because the claim sets of the two parties were not directed to the same patentable invention in accordance with the PTAB's two-way test for patent interferences.

Casebia Therapeutics, LLP and Subsidiary

Consolidated Financial Statements
As of December 31, 2016 and the Period From February 12, 2016 (Inception) Through December 31, 2016

Casebia Therapeutics, LLP and subsidiary

Consolidated financial statements as of December 31, 2016 and the period from February 12, 2016 (inception) through December 31, 2016	Pages
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Consolidated statement of cash flows	S-5
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Report of Independent Auditors

The Management Board and Stockholders
Casebia Therapeutics LLP

We have audited the accompanying consolidated financial statements of Casebia Therapeutics LLP and subsidiary, which comprise the consolidated balance sheet as of December 31, 2016, and the related consolidated statements of operations, comprehensive loss, changes in partners' equity, and cash flows for the period from February 12, 2016 (inception) through December 31, 2016, and the related consolidated notes to the consolidated financial statements.

Management's Responsibility for the Financial Statements

Management is responsible for the preparation and fair presentation of these financial statements in conformity with U.S. generally accepted accounting principles; this includes the design, implementation and maintenance of internal control relevant to the preparation and fair presentation of financial statements that are free of material misstatement, whether due to fraud or error.

Auditor's Responsibility

Our responsibility is to express an opinion on these financial statements based on our audit. We conducted our audit in accordance with auditing standards generally accepted in the United States. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers internal control relevant to the entity's preparation and fair presentation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. Accordingly, we express no such opinion. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of significant accounting estimates made by management, as well as evaluating the overall presentation of the financial statements.

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

Opinion

In our opinion, the financial statements referred to above present fairly, in all material respects, the (consolidated) financial position of Casebia Therapeutics, LLP and subsidiary at December 31, 2016, and the consolidated results of their operations and their cash flows for the period from February 12, 2016 (inception) through December 31, 2016 in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 10, 2017

Casebia Therapeutics, LLP and subsidiary
Consolidated balance sheet

	December 31, 2016
Assets	
Current assets:	
Cash	$ 2,216,490
Prepaid assets	36,948
Tenant improvement allowance receivable	1,299,007
Total current assets	3,552,445
Property and equipment, net	4,560,488
Restricted cash	1,225,768
Total assets	$ 9,338,701
Liabilities and Equity	
Current liabilities:	
Accounts payable	$ 397,441
Due to partners	1,881,160
Deferred rent	722,977
Accrued expenses	302,137
Total current liabilities	3,303,715
Deferred rent	5,043,355
Total liabilities	8,347,070
Commitments and contingencies	
Partners' Equity:	
Partners' equity	60,991,631
Contribution receivable from partner	(60,000,000)
Total partners' equity	991,631
Total liabilities and partners' equity	$ 9,338,701

See accompanying notes to consolidated financial statements.

Casebia Therapeutics, LLP and subsidiary
Consolidated statement of operations and comprehensive loss

	Period from February 12, 2016 (inception) through December 31, 2016
Operating expenses:	
General and administrative (includes $1,157,496 of expenses from related parties)	$ 3,458,074
Research and development (includes $4,879,971 of expenses from related parties)	77,373,590
Total operating expenses	80,831,664
Loss from operations	(80,831,664)
Net loss and comprehensive loss	$ (80,831,664)

See accompanying notes to consolidated financial statements.

Casebia Therapeutics, LLP and subsidiary
Consolidated statement of cash flows

	Period from February 12, 2016 (inception) through December 31, 2016
Cash flows from operating activities:	
Net loss	$ (80,831,664)
Adjustments to reconcile net loss to net cash used in operating activities:	
Depreciation and amortization	7,329
Equity-based compensation expense	152,270
Non-cash contributions by partners	199,347
Deferred rent expense	374,132
Contribution of in-process research and development	36,371,678
Changes in operating assets and liabilities:	
Prepaid expenses	(36,948)
Restricted cash	(1,225,768)
Accounts payable	372,258
Due to partners	1,881,160
Accrued expenses	297,137
Net cash used in operating activities	(42,439,069)
Cash flows from investing activities:	
Additions to property and equipment	(444,441)
Net cash used in investing activities	(444,441)
Cash flows from financing activities:	
Capital contributions from partners	45,100,000
Net cash provided by financing activities	45,100,000
Net increase in cash	2,216,490
Cash, beginning of period	—
Cash, end of period	$ 2,216,490
Non-cash investing activities:	
Purchases of property and equipment included in accounts payable and accrued expenses	$ 30,183
Property and equipment additions acquired under tenant improvement allowance	$ 4,093,193
Non-cash financing activities:	
Capital contribution receivable from partner	$ 60,000,000
Contribution of in-process research and development from partner	$ 36,371,678
Non-cash contributions from partners	$ 199,347

See accompanying notes to consolidated financial statements.

Casebia Therapeutics, LLP and subsidiary
Consolidated statement of changes in partners' equity

	Partners' equity	Contribution receivable from partner	Total Partners' equity
Balance at February 12, 2016 (inception)	$ —	$ —	$ —
Contributions from partners	105,100,000	—	105,100,000
Contribution of in-process research and development from partner	36,371,678	—	36,371,678
Net loss	(80,831,664)	—	(80,831,664)
Partner equity-based compensation	152,270	—	152,270
Other non-cash contributions by partners	199,347	—	199,347
Contribution receivable from partner (See Note 6)	—	(60,000,000)	(60,000,000)
Balance at December 31, 2016	$ 60,991,631	$ (60,000,000)	$ 991,631

See accompanying notes to consolidated financial statements.

1. Organization and Operations

Organization

Casebia Therapeutics, LLP (the "JV" or "Casebia") is a joint venture formed between CRISPR Therapeutics AG ("CRISPR") and Bayer HealthCare LLC ("Bayer HealthCare") in February, 2016 to research the development of new therapeutics to cure blood disorders, blindness and congenital heart disease. Bayer HealthCare and CRISPR each received a 50% equity interest in the entity in exchange for their contributions to Casebia. CRISPR contributed $0.1 million in cash and licensed its proprietary CRISPR/Cas9 gene editing technology and intellectual property for selected disease indications. Bayer HealthCare has contributed its protein engineering expertise and relevant disease know-how. Bayer HealthCare will also provide up to $300.0 million in research and development funding to Casebia over the first five years, subject to certain conditions. The activities of Casebia are controlled by a Management Board under the joint control of CRISPR and Bayer HealthCare.

Liquidity

Casebia's net loss for 2016 was $80.8 million. As of December 31, 2016, Casebia had unrestricted cash of $2.2 million. In January, 2017, according to the terms of the Joint Venture Agreement between CRISPR and Bayer HealthCare (the "JV Agreement"), following the December 2016 receipt of consents necessary from patent holders of CRISPR's intellectual property, Bayer HealthCare made a capital contribution to Casebia of $60.0 million, which is recorded as a contribution receivable in the accompanying consolidated balance sheet. Casebia believes that its cash as of December 31, 2016, along with the capital contribution received in January 2017, will be sufficient to fund its current operating plan for at least the next 12 months.

The JV Agreement sets forth the initial 24-month budget for Casebia, which will be revised by the Management Board on a yearly basis for the following 24 months. Bayer HealthCare, subject to certain conditions, is solely responsible for providing Casebia with the necessary additional funding as determined by the Management Board until the earlier of (i) its aggregate remaining commitment amount of $255.0 million as of December 31, 2016 is fully funded, at which point all additional financing must be approved by the Management Board or (ii) the termination of the JV Agreement in accordance with its terms. Any additional funding beyond the amounts initially committed by Bayer HealthCare in the JV Agreement up to the $300.0 million aggregate commitment amount, whether for purposes of an acquisition or otherwise, will not affect or dilute CRISPR's 50% interest in Casebia.

There can be no assurances, however, that Casebia's current operating plan will be achieved or that additional funding will be available on acceptable terms to Casebia, or at all.

2. Summary of significant accounting policies

Basis of presentation and consolidation

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"), and include the accounts of Casebia and its subsidiary. All intercompany accounts and transactions have been eliminated. Any reference in these notes to applicable guidance is meant to refer to the authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASUs") of the Financial Accounting Standards Board ("FASB").

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. On an ongoing basis, Casebia's management evaluates its estimates, which include, but are not limited to, equity-based compensation expense and reported amounts of expenses during the reporting period. In addition, significant estimates in these consolidated financial statements have been made in connection with the calculation of the value of contributed technology and research and development expenses. Casebia bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Actual results may differ from those estimates or assumptions.

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. Casebia's chief operating decision maker, the chief executive officer, views Casebia's operations and manages its business in one operating segment which is the business of researching the development of new breakthrough therapeutics to cure blood disorders, blindness and congenital heart disease.

Cash

Casebia considers all highly liquid investments with maturities of 90 days or less from the purchase date to be cash equivalents. As of December 31, 2016, Casebia had no cash equivalents. All cash was held in depository accounts and is reported at fair value.

Concentrations of Credit Risk and Off-balance Sheet Risk

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

Property and equipment

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

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

Research and Development Expenses

Research and development costs, which include employee compensation costs, facilities, lab supplies and materials, overhead, preclinical development, and other related costs, are charged to expense as incurred.

Operating Leases

Casebia leases office and laboratory facilities under non-cancelable operating lease agreements. The lease agreements contain free or escalating rent payment provisions. Casebia recognizes rent expense under such leases on a straight-line basis over the term of the lease with the difference between the expense and the payments recorded as deferred rent on the consolidated balance sheet. Amounts received from lessors are accounted for as lease incentives, which are amortized as a reduction of rent expense over the term of the lease. Lease renewal periods are considered on a lease-by-lease basis in determining the lease term.

Equity-based Compensation Expense

Certain employees of Casebia have been granted options to purchase CRISPR common stock. In accordance with FASB ASC Topic 323-10, Investments – Equity Method and Joint Ventures ("ASC 323-10"), CRISPR expenses the cost of the stock options granted to employees of Casebia as incurred. Concurrently, Casebia will also recognize the same cost of the stock options as an expense and capital contribution from CRISPR.

CRISPR accounts for stock options issued to non-employees under FASB ASC Topic 505-50, Equity-Based Payments to Non-Employees ("ASC 505-50"). As such, the value of such options is periodically remeasured and income or expense is recognized over their vesting terms. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method. CRISPR estimates the fair value of stock options using the Black-Scholes option pricing model.

The Black-Scholes option pricing model requires the input of certain subjective assumptions, including (i) the expected share price volatility, (ii) the calculation of expected term of the award, (iii) the risk-free interest rate and (iv) the expected dividend yield. Due to the lack of sufficient public market data for the trading of CRISPR's Common Shares and a lack of CRISPR-specific historical and implied volatility data, CRISPR has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The group of representative companies have characteristics similar to CRISPR, including stage of product development and focus on the life science industry. For options granted to non-employees, CRISPR utilizes the contractual term of the arrangement as the basis for the expected term assumption. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. CRIPSR uses an assumed dividend yield of zero as CRISPR has never paid dividends and has no current plans to pay any dividends on its Common Shares.

CRISPR measures equity-based compensation awards granted to non-employees at fair value as the awards vest and recognizes the resulting value as compensation expense at each financial reporting period.

Patent Costs

Costs to secure and prosecute patent application and other legal costs related to the protection of Casebia's intellectual property are expensed as incurred, and are classified as general and administrative expenses in Casebia's consolidated statements of operations.

Income taxes

Casebia is a limited liability partnership. No provision for federal income taxes is necessary in the financial statements of Casebia because, as a partnership, it is not subject to federal income tax and the tax effect of its activities accrues to the partners.

In certain circumstances, partnerships may be held to be associations taxable as corporations. The Internal Revenue Service has issued regulations specifying circumstances under current law when such a finding may be made, and management has obtained an opinion of counsel based on those regulations that the partnership is not an association taxable as a corporation. A finding that the partnership is an association taxable as a corporation could have a material adverse effect on the financial position and results of operations of the partnership.

Fair value of financial instruments

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

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

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

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

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

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

The fair value of the CRISPR license which was written off following the formation of Casebia was calculated based on the consideration paid and the fair value of CRISPR's 50% interest in Casebia as of February 12, 2016, which was determined utilizing discounted cash flows based on reasonable estimates and assumptions of cash flows expected from Casebia, and thus considered a Level 3 input. The value of the intellectual property contributed by CRISPR was determined to be $36.4 million.

The carrying amount of accounts payable and accrued expenses as reporting in the consolidated balance sheet as of December 31, 2016 approximate fair value due to the short-term duration of these instruments. Casebia may elect to measure financial instruments and certain other items at specified election dates in the future.

Comprehensive Loss

Comprehensive loss consists of net loss and changes in equity during the period from transactions and other events and circumstances generated from non-owner sources. Casebia's net loss equals comprehensive loss for the year ended December 31, 2016.

Subsequent Events

Casebia considers events or transactions that occur after the balance sheet date but prior to the date the financial statements are available to be issued for potential recognition or disclosure in the financial statements. Casebia has completed an evaluation of all subsequent events after the audited balance sheet date of December 31, 2016 through March 10, 2017, to ensure that these financial statements include appropriate disclosure of events recognized in the financial statements as of December 31, 2016, and events which occurred subsequently but were not recognized in the financial statements.

Recent Accounting Pronouncements

In May 2014, the FASB issued ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606) ("ASU 2014-09"). Subsequently, the FASB also issued ASU No. 2015-14, Revenue from Contracts with Customers (Topic 606), which adjusted the effective date of ASU 2014-09; ASU No. 2016-08, Revenue from Contracts with Customers (Topic 606): Principal versus Agent Considerations (Reporting Revenue Gross versus Net), which amends the principal-versus-agent implementation guidance and illustrations in ASU 2014-09; ASU No. 2016-10, Revenue from Contracts with Customers (Topic 606): Identifying Performance Obligations and Licensing, which clarifies identifying performance obligation and licensing implementation guidance and illustrations in ASU 2014-09; and ASU No. 2016-12, Revenue from Contracts with Customers (Topic 606): Narrow-Scope Improvements and Practical Expedients, which addresses implementation issues and is intended to reduce the cost and complexity of applying the new revenue standard in ASU 2014-09 (collectively, the "Revenue ASUs").

The Revenue ASUs provide an accounting standard for a single comprehensive model for use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance. The accounting standard is effective for interim and annual periods beginning after December 15, 2017, with an option to early adopt for interim and annual periods beginning after December 15, 2016. The guidance permits two methods of adoption: retrospectively to each prior reporting period presented (the full retrospective method), or retrospectively with the cumulative effect of initially applying the guidance recognized at the date of initial application (the modified retrospective method). Casebia currently anticipates adoption of the new standard effective January 1, 2018 under the full retrospective method. Casebia is currently assessing all potential impacts of the standard on its consolidated financial statements.

In August 2014, the FASB issued ASU No. 2014-15, Presentation of Financial Statements—Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's ability to Continue as a Going Concern ("ASU 2014-15"), which requires management to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. This guidance is effective for the annual reporting period ending after December 15, 2016 and for annual and interim periods thereafter. Casebia adopted ASU 2014-15 on December 31, 2016 and the adoption of ASU 2014-15 did not have an effect on its consolidated financial statements or disclosures.

In February 2016, the FASB issued ASU No. 2016-02, Leases ("ASU 2016-02"), which applies to all leases and will require lessees to record most leases on the balance sheet, but recognize expense in a manner similar to the current standard. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 and interim periods within those years, which is the year ended December 31, 2019 for Casebia. Entities are required to use a modified retrospective approach of adoption for leases that exist or are entered into after the beginning of the earliest comparative period in the financial statements. Full retrospective application is prohibited. Casebia is evaluating the new guidance and the expected effect on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, Compensation—Stock Compensation (Topic 718) ("ASU 2016-09"). The guidance changes how companies account for certain aspects of equity-based payments to employees. Entities will be required to recognize income tax effects of awards in the income statement when the awards vest or are settled. The guidance also allows an employer to repurchase more of an employee's shares than it can under current guidance for tax withholding purposes providing for withholding at the employee's maximum rate as opposed to the minimum rate without triggering liability accounting and to make a policy election to account for forfeitures as they occur. The updated guidance is effective for annual periods beginning after December 15, 2017. Early adoption is permitted. The adoption of this standard is not expected to have a material impact on the Casebia's financial position, results of operations or statements of cash flows upon adoption, primarily because as a partnership, Casebia is not subject to federal income tax and the tax effect of its activities accrues to the partners.

In November, 2016, the FASB issued ASU No. 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash ("ASU 2016-18"). ASU 2016-18 requires that a statement of cash flows explain the change during the period in the total cash, cash equivalents, and amounts generally described as restricted cash or restricted cash equivalents. Therefore, amounts generally described as restricted cash and restricted cash equivalents should be included with cash and cash equivalents when reconciling the beginning and ending balances shown on the statement of cash flows. The guidance is effective for annual periods beginning after December 15, 2017 and early adoption is permitted. ASU 2016-18 must be applied retrospectively to all periods presented. Upon adoption, the 2016 period in Casebia's three-year statements of cash flows will reflect an increase in operating cash flows from the increase in restricted cash during 2016. Casebia does not expect any additional impact on our financial statements.

3. Property and Equipment, net

Property and equipment, net, consists of the following:

	As of December 31, 2016
Construction work in process	$ 4,400,427
Laboratory equipment	151,828
Computer hardware	15,562
	4,567,817
Accumulated Depreciation	(7,329)
Property and equipment, net	$ 4,560,488

Depreciation expense for the period from February 12, 2016 (inception) through December 31, 2016 was $7,329.

4. Accrued Expenses

Accrued expenses consist of the following:

	As of December 31, 2016
Professional fees	$ 225,438
Payroll and employee-related costs	76,699
Total	$ 302,137

5. Commitments and Contingencies

Operating Leases

In August, 2016, Casebia entered into an agreement with Pfizer, Inc. to sublease 32,688 square feet of office and laboratory space in Cambridge, MA. The sublease commenced in October, 2016, expires in March, 2024 and includes a tenant improvement allowance of $5.4 million, of which Casebia has recorded $4.1 million as leasehold improvements and $1.3 million as tenant improvement allowance receivable at December 31, 2016. Casebia has the option to extend the term of the sublease by five years.

The future minimum payments for non-cancelable leases as of December 31, 2016 is as follows:

Year Ending December 31,	
2017	$ 1,838,700
2018	2,506,761
2019	2,582,025
2020	2,659,577
2021	2,739,418
Thereafter	6,459,639
Total	$ 18,786,120

In April 2016, Casebia entered into a $1.2 million letter of credit to secure its obligations under this sublease. The letter of credit is secured by cash held in a restricted depository account.

In addition, during 2016 Casebia occupied a portion of CRISPR's and Bayer HealthCare's office and laboratory space, for which Casebia was not charged rent. Casebia estimated noncash expense for these spaces of $9,792 for 2016, which is recorded as Non-cash Contributions from Partners in the accompanying consolidated balance sheet.

Total rent expense for the period from February 12, 2016 (inception) through December 31, 2016 was $383,924.

6. Joint Venture Agreement

On December 19, 2015, CRISPR and Bayer HealthCare entered into an agreement to establish Casebia with the purpose of researching the development of new therapeutics to cure blood disorders, blindness and congenital heart disease. On February 12, 2016, CRISPR and Bayer HealthCare completed the formation of Casebia, a limited liability partnership formed in the United Kingdom. Bayer HealthCare and CRISPR each received a 50% equity interest in the entity in exchange for their contributions to the entity. CRISPR contributed $0.1 million in cash and licensed its proprietary CRISPR/Cas9 gene editing technology and intellectual property for selected disease indications. Bayer HealthCare has also contributed its protein engineering expertise and relevant disease know-how.

Bayer HealthCare is committed to provide up to $300.0 million in research and development funding to Casebia over the first five years, subject to certain conditions, the first $45.0 million of which was contributed upon formation in the first quarter of 2016 and an additional $60.0 million of which was contributed in January, 2017, following the December, 2016 receipt of consents necessary from patent holders of CRISPR's intellectual property, which is recorded as a contribution receivable in the accompanying consolidated balance sheet. Under the joint venture agreement, CRISPR has no obligation to provide any additional funding and CRISPR's ownership interest will not be diluted from future contributions from Bayer. The activities of Casebia are controlled by a Management Board under the joint control of CRISPR and Bayer HealthCare.

CRISPR and Bayer HealthCare will also provide to Casebia compensated services through separate agreements.

Under the JV Agreement, Casebia has paid CRISPR $35.0 million in exchange for a worldwide, exclusive license to commercialize CRISPR's CRISPR/Cas9 technology specifically for the indications designated by Casebia. In March 2016, Casebia paid a non-refundable up-front payment of $20.0 million as a technology access fee. The remaining $15.0 million was paid on December 22, 2016 following delivery of the consents necessary from patent holders of CRISPR's intellectual property. There are no milestone, royalty or other payments due to CRISPR under this aspect of the agreement.

The fair value of the license was calculated to be $71.4 million based on the consideration paid and the fair value of the 50% interest in Casebia, which was determined utilizing discounted cash flows based on reasonable estimates and assumptions of cash flows expected from Casebia. As Casebia only paid $35.0 million in cash to acquire the license, the remaining $36.4 million of fair value received was accounted for as contributed capital from CRISPR. Casebia determined that the contribution of the intellectual property represented an acquisition of in-process research and development with no alternative future use, which was expensed to research and development expenses at the time of its contribution in accordance with ASC 730, Research and Development.

The JV Agreement can be terminated by Bayer HealthCare and CRISPR upon mutual written consent. Either party may terminate the JV Agreement in the event of specified breaches by the other party or in the event the other party becomes subject to specified bankruptcy, winding up or similar circumstances. Either party may also terminate upon a change of control of the other party, as defined in the JV Agreement. Bayer HealthCare also has the right to terminate in the event (i) CRISPR is not able to maintain

the intellectual property rights licensed to Casebia pursuant to the CRISPR IP Contribution Agreement or (ii) CRISPR has not achieved preclinical proof of concept with a CRISPR/Cas9 product candidate in a specified period of time.

The JV Agreement may also be terminated by either party if, subsequent to the time that Bayer HealthCare has funded its entire $300.0 million commitment, the Management Board is unable to approve and obtain sufficient funding, within the time specified in the JV Agreement, to continue Casebia's operations for the next 18 months.

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

7. Equity-based Compensation

Certain employees of Casebia have been granted options to purchase CRISPR common stock. Terms of the equity awards, including vesting requirements, are determined by CRISPR's Board of Directors, subject to the provisions of CRISPR's stock option plans. Options granted by CRISPR typically vest over four years and have a contractual life of ten years. In accordance with ASC 323-10, CRISPR expenses the cost of the stock options granted to employees of Casebia as incurred. CRISPR accounts for these options in accordance with ASC 505-50. As such, the value of such options is periodically remeasured and income or expense and is recognized by CRISPR over their vesting terms. Concurrently, Casebia will also recognize the same cost of the stock options as expense and a capital contribution from CRISPR. Compensation cost related to awards with service-based vesting schedules is recognized using the straight-line method.

Equity-based Compensation Expense

Total equity-based compensation expense is recognized for stock options granted to employees and has been reported in Casebia's consolidated statement of operations as follows:

	Period from February 12, 2016 (inception) through December 31, 2016
Research and development	$ 97,117
General and administrative	55,153
Total	$ 152,270

Stock Option Awards

The following table summarizes stock option activity for CRISPR stock options granted to employees of Casebia:

	Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Outstanding at February 12, 2016 (inception)	—			
Granted	336,353	$ 13.19		
Exercised	—			
Cancelled or forfeited	—			
Outstanding at December 31, 2016	336,353	$ 13.19	9.5	$ 2,377,144
Exercisable at December 31, 2016	42,726	$ 1.85	8.7	$ 786,769
Vested or expected to vest at December 31, 2016(1)	311,168	$ 12.94	9.5	$ 2,275,950

(1) Represents the number of vested options at December 31, 2016 plus the number of unvested options expected to vest based on the unvested options outstanding at December 31, 2016.

The fair value of options vested from February 12, 2016 (inception) through December 31, 2016 was $0.2 million. The weighted-average grant date fair values of stock options granted from February 12, 2016 (inception) through December 31, 2016 was $18.17. As of December 31, 2016, the total unrecognized compensation cost related to CRISPR stock options was $4.7 million. The total unrecognized compensation cost will be adjusted for future forfeitures. As of December 31, 2016, Casebia expects to recognize total unrecognized compensation cost over a remaining weighted-average period of 3.4 years.

CRISPR estimates the fair value of each stock award on the grant date using the Black-Scholes option-pricing model based on the following range of assumptions regarding the fair value of the underlying Common Shares on each measurement date:

	Period from February 12, 2016 (inception) through December 31, 2016
Weighted average expected volatility	88.2%
Expected term (in years)	9.5
Risk free interest rate	2.3%
Expected dividend yield	0.0%

8. Related Party Transactions

Bayer HealthCare has agreed to provide to Casebia certain protein engineering knowhow as well as other administrative services. From February 12, 2016 (inception) through December 31, 2016, Casebia recorded $3.8 million and $1.1 million of expense related to these activities to research and development and general and administrative expenses, respectively, $1.1 million of which is included in Due to Partners in the accompanying balance sheet at December 31, 2016. Included in the above expenses, Bayer HealthCare provided management services to Casebia during 2016 that were not billed to Casebia. These expenses, totaling $189,555, were treated as a capital contribution in the accompanying financial statements.

CRISPR has also agreed to provide Casebia with certain general and administrative and research and development services and Casebia has recorded expense from February 12, 2016 (inception) through December 31, 2016 related to those services of $1.1 million and $0.1 million to research and development and general and administrative expenses, respectively, $0.8 million of which is included in Due to Partners in the accompanying balance sheet at December 31, 2016.

All amounts due to Partners are due within 30 days of receipt of the respective invoices.

9. Income Taxes

Casebia is a pass through entity for federal and state income tax purposes and generally does not incur income taxes. Instead, its earnings and losses are included in the income tax returns of the partners.

10. Employee Benefit Plan

Casebia maintains a defined contribution 401(k) plan (the “Plan”) in which substantially all of its permanent employees are eligible to participate. Employee contributions are voluntary and are determined on an individual basis, limited by the maximum amounts allowable under federal tax regulations. The Company makes matching contributions of 100% of the first 3% and 50% of the next 2% of employees’ contributions to the Plan. Casebia recorded employer contribution expense of $2,622 for the period from February 12, 2016 (inception) through December 31, 2016.

Exhibit Index

Exhibit Number	Description
3.1	Articles of Association (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K filed on November 8, 2016).
4.1	Subscription Agreement, dated December 19, 2015, by and between CRISPR Therapeutics AG and Bayer Global Investments B.V. (incorporated herein by reference to Exhibit 4.1 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.1†	Joint Venture Agreement, dated December 19, 2015, between CRISPR Therapeutics AG and Bayer HealthCare LLC (incorporated herein by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.2†	IP Contribution Agreement, dated March 16, 2016, by and between CRISPR Therapeutics AG, Bayer HealthCare LLC and Casebia Therapeutics LLP (incorporated herein by reference to Exhibit 10.2 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.3†	Option Agreement, dated March 16, 2016, by and between CRISPR Therapeutics AG, Bayer HealthCare LLC and Casebia Therapeutics LLP (incorporated herein by reference to Exhibit 10.3 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.4†	Strategic Collaboration, Option and License Agreement, dated October 26, 2015, by and among CRISPR Therapeutics AG, CRISPR Therapeutics Limited, CRISPR Therapeutics, Inc., TRACR Hematology Limited, Vertex Pharmaceuticals, Incorporated and Vertex Pharmaceuticals (Europe) Limited (incorporated herein by reference to Exhibit 10.4 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.5†	License Agreement, dated April 15, 2014, by and between CRISPR Therapeutics AG and Emmanuelle Marie Charpentier (incorporated herein by reference to Exhibit 10.5 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.6†	License Agreement, dated April 15, 2014, by and between TRACR Hematology Limited and Emmanuelle Marie Charpentier (incorporated herein by reference to Exhibit 10.6 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.7†	Patent Assignment Agreement, dated November 7, 2014, by and between CRISPR Therapeutics AG, Emmanuelle Marie Charpentier, the University of Vienna and Ines Fonfara (incorporated herein by reference to Exhibit 10.7 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.8	Form of Indemnification Agreement (incorporated herein by reference to Exhibit 10.8 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.9	Registration Rights Agreement, dated June 10, 2016, by and among CRISPR Therapeutics AG and certain shareholders (incorporated herein by reference to Exhibit 10.9 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.10#	Employment Agreement, dated October 6, 2016, by and between CRISPR Therapeutics AG and Rodger Novak (incorporated herein by reference to Exhibit 10.10 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.11#	Amended and Restated Employment Agreement, dated October 6, 2016, by and between CRISPR Therapeutics, Inc. and Marc A. Becker (incorporated herein by reference to Exhibit 10.11 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.12#	Employment Agreement, dated October 6, 2016, by and between CRISPR Therapeutics, Inc. and Samarth Kulkarni (incorporated herein by reference to Exhibit 10.12 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).
10.13#	Amended and Restated Employment Agreement, dated October 6, 2016, by and between CRISPR Therapeutics, Inc. and Sven Ante Lundberg (incorporated herein by reference to Exhibit 10.13 to the Company's Registration Statement on Form S-1 filed on October 7, 2016).

Exhibit Number	Description
10.14#	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).
10.15#	CRISPR Therapeutics AG 2016 Stock Option and Incentive Plan (incorporated herein by reference to Exhibit 10.15 to the Company's Registration Statement on Form S-1 filed on September 9, 2016).
10.16#	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).
10.17	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).
10.18†	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).
21.1*	Subsidiaries of the Registrant
23.1*	Consent of Ernst & Young LLP
23.2*	Consent of Ernst & Young LLP – Casebia Therapeutics, LLP
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

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

Exhibit 21.1

Subsidiaries of the Registrant

Name of Subsidiary	Jurisdiction of Incorporation or Organization
CRISPR Therapeutics, Inc.	Delaware
CRISPR Therapeutics Ltd.	United Kingdom

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-214184) pertaining to the CRISPR Therapeutics AG 2015 Stock Option and Grant Plan, the CRISPR Therapeutics AG 2016 Stock Option and Incentive Plan, the CRISPR Therapeutics AG 2016 Employee Stock Purchase Plan, the Non-Qualified Option Agreement with Megan Menner, the Non-Qualified Option Agreement with Paul Schneider, and the Non-Qualified Option Agreement with Pablo Cagnoni of CRISPR Therapeutics AG of our report dated March 10, 2017, with respect to the consolidated financial statements of CRISPR Therapeutics AG included in this Annual Report (Form 10-K) for the year ended December 31, 2016.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 10, 2017

Exhibit 23.2

CONSENT OF INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-214184) pertaining to the CRISPR Therapeutics AG 2015 Stock Option and Grant Plan, the CRISPR Therapeutics AG 2016 Stock Option and Incentive Plan, the CRISPR Therapeutics AG 2016 Employee Stock Purchase Plan, the Non-Qualified Option Agreement with Megan Menner, the Non-Qualified Option Agreement with Paul Schneider, and the Non-Qualified Option Agreement with Pablo Cagnoni of CRISPR Therapeutics AG of our report dated March 10, 2017, with respect to the consolidated financial statements of Casebia Therapeutics LLP, included in the Annual Report (Form 10-K) of CRISPR Therapeutics AG for the year ended December 31, 2016.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 10, 2017

Exhibit 31.1

CERTIFICATIONS

I, Rodger Novak, certify that:

1. I have reviewed this Annual Report on Form 10-K of CRISPR Therapeutics AG;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 10, 2017

/s/ Rodger Novak

Rodger Novak
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, Marc Becker, certify that:

1. I have reviewed this Annual Report on Form 10-K of CRISPR Therapeutics AG;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

March 10, 2017

/s/ Marc Becker

Marc Becker
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

**CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report on Form 10-K of CRISPR Therapeutics AG (the "Company") for the year ended December 31, 2016, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned officers hereby certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350, that to the best of his or her knowledge:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 10, 2017

/s/ Rodger Novak

Rodger Novak
Chief Executive Officer
(Principal Executive Officer)

Date: March 10, 2017

/s/ Marc Becker

Marc Becker
Chief Financial Officer
(Principal Financial and Accounting Officer)